SUBSTITUTED BIARYL ETHER COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to methods for treating hair loss in mammals, including arresting and / or reversing hair loss and promoting hair growth.

BACKGROUND OF THE INVENTION

Hair loss is a common problem which occurs, for example, through natural processes or is often chemically promoted through the use of certain therapeutic drugs designed to alleviate conditions such as cancer. Often such hair loss is accompanied by lack of hair regrowth which causes partial or full baldness.

As is well-known in the art, hair growth occurs by a cycle of activity which involves alternating periods of growth and rest. This cycle is often divided into three main stages which are known as anagen, catagen, and telogen. Anagen is the growth phase of the cycle and may be characterized by penetration of the hair follicle deep into the dermis with rapid proliferation of cells which are differentiating to form hair. The next phase is catagen, which is a transitional stage marked by the cessation of cell division, and during which the hair follicle regresses through the dermis and hair growth is ceased. The next phase, telogen, is often characterized as the resting stage during which the regressed follicle contains a germ with tightly packed dermal papilla cells. At telogen, the initiation of a new anagen phase is caused by rapid cell proliferation in the germ, expansion of the dermal papilla, and elaboration of basement membrane components. Wherein hair growth ceases, most of the hair follicles reside in telogen and anagen is not engaged, thus causing the onset of full or partial baldness.

There have been many attempts in the literature to invoke the regrowth of hair by, for example, the promotion or prolongation of anagen. Currently, there are two drugs approved by the United States Food and Drug Administration for the treatment of male pattern baldness: topical minoxidil (marketed as Rogaine® by Pharmacia & Upjohn), and oral finasteride (marketed as Propecia® by Merck & Co., Inc.). For several reasons, however, including safety concerns and / or lack of efficacy, the search for efficacious hair growth inducers is ongoing.

Interestingly, it is known that the thyroid hormone known as thyroxine ("T4") converts to thyronine ("T3") in human skin by deiodinase I, a selenoprotein. Selenium deficiency causes a decrease in T3 levels due to a decrease in deiodinase I activity; this reduction in T3 levels is strongly associated with hair loss. Consistent with this observation, hair growth is a reported

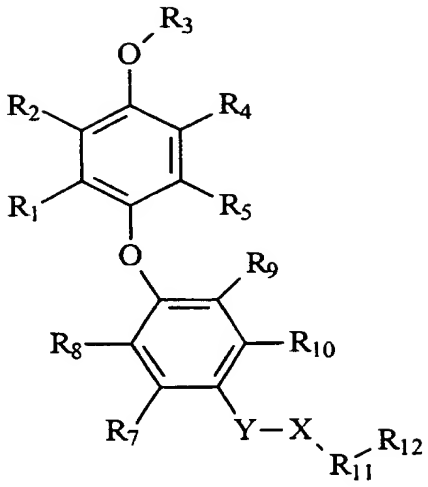
side effect of administration of T4. See, e.g., Berman, "Peripheral Effects of L-Thyroxine on Hair Growth and Coloration in Cattle", *Journal of Endocrinology*, Vol. 20, pp. 282 - 292 (1960); and Gunaratnam, "The Effects of Thyroxine on Hair Growth in the Dog", *J. Small Anim. Pract.*, Vol. 27, pp. 17 - 29 (1986). Furthermore, T3 and T4 have been the subject of several patent publications relating to treatment of hair loss. See, e.g., Fischer et al., DE 1,617,477, published January 8, 1970; Mortimer, GB 2,138,286, published October 24, 1984; and Lindenbaum, WO 96/25943, assigned to Life Medical Sciences, Inc., published August 29, 1996.

Unfortunately, however, administration of T3 and / or T4 to treat hair loss is not practicable because these thyroid hormones are also known to induce significant cardiotoxicity. See, e.g., Walker et al., U.S. Patent No. 5,284,971, assigned to Syntex, issued February 8, 1994 and Emmett et al., U.S. Patent No. 5,061,798, assigned to Smith Kline & French Laboratories, issued October 29, 1991. Surprisingly, the present inventors have discovered compounds which strongly initiate hair growth without inducing cardiotoxicity. Consistent with this discovery, but without intending to be limited by theory, the present inventors have surprisingly discovered that the preferred compounds of the present invention interact strongly with hair-selective thyroid hormone receptors but interact less strongly, or not at all, with heart-selective hormone receptors. These unique properties are, of course, not shared with T3 and / or T4. Accordingly, the compounds and compositions herein are useful for treating hair loss, including arresting and / or reversing hair loss and promoting hair growth.

SUMMARY OF THE INVENTION

The present invention relates to compounds and compositions which are particularly useful for treating hair loss in mammals, including arresting and / or reversing hair loss and promoting hair growth.

The compounds of the present invention have the structure:



and pharmaceutically acceptable salts, hydrates, and biohydrolyzable amides, esters, and imides thereof, wherein R_1, R_2, R_3, R_4, R_5, R_7, R_8, R_9, R_{10}, Y, X, R_{11}, and R_{12} are defined herein.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds and compositions which are particularly useful for treating hair loss in mammals, including arresting and / or reversing hair loss and promoting hair growth.

In addition to discovering that the present compounds are useful for treating hair loss, the present inventors have also surprisingly discovered that the preferred compounds of the present invention are cardiac-sparing.

Publications and patents are referred to throughout this disclosure. All references cited herein are hereby incorporated by reference.

All percentages, ratios, and proportions used herein are by weight unless otherwise specified.

In the description of the invention various embodiments and/or individual features are disclosed. As will be apparent to the ordinarily skilled practitioner all combinations of such embodiments and features are possible and can result in preferred executions of the invention.

As used herein, wherein any variable, moiety, group, or the like occurs more than one time in any variable or structure, its definition at each occurrence is independent of its definition at every other occurrence.

Definition and Usage of Terms

The following is a list of definitions for terms used herein:

As used herein "salt" is a cationic salt formed at any acidic (*e.g.*, carboxyl) group, or an anionic salt formed at any basic (*e.g.*, amino) group. Many such salts are known in the art. Preferred cationic salts include the alkali metal salts (such as, for example, sodium and potassium), alkaline earth metal salts (such as, for example, magnesium and calcium), and organic salts. Preferred anionic salts include the halides (such as, for example, chloride salts). Such acceptable salts must, when administered, be appropriate for mammalian use.

As used herein, "alkenyl" is an unsubstituted or substituted hydrocarbon chain radical having from 2 to about 15 carbon atoms; preferably from 2 to about 10 carbon atoms; more preferably from 2 to about 8 carbon atoms, and most preferably from about 2 to about 6 carbon atoms. Alkenyls have at least one olefinic double bond. Non-limiting examples of alkenyls include vinyl, allyl, and butenyl.

As used herein, "alkoxy" is an oxygen radical having an alkyl, alkenyl, or alkynyl, preferably an alkyl or alkenyl, and most preferably an alkyl substituent. Examples of alkoxy radicals include -O-alkyl and -O-alkenyl. An alkoxy radical may be substituted or unsubstituted.

As used herein, "aryloxy" is an oxygen radical having an aryl substituent. An aryloxy radical may be substituted or unsubstituted.

As used herein, "alkyl" is an unsubstituted or substituted saturated hydrocarbon chain radical having from 1 to about 15 carbon atoms; preferably from 1 to about 10 carbon atoms; more preferably from 1 to about 6 carbon atoms; and most preferably from 1 to about 4 carbon atoms. Preferred alkyls include, for example, methyl, ethyl, propyl, *iso*-propyl, and butyl.

As used herein, "alkylene" refers to an alkyl, alkenyl, or alkynyl which is a diradical. For example, "methylene" is $-CH_2-$. Alkylenes may be substituted or unsubstituted.

As used herein, "alkynyl" is an unsubstituted or substituted hydrocarbon chain radical having from 2 to about 15 carbon atoms; preferably from 2 to about 10 carbon atoms; more preferably from 2 to about 8 carbon atoms, and most preferably from about 2 to about 6 carbon atoms. Alkynyls have at least one triple bond.

As used herein, "aryl" is an aromatic ring radical which is either carbocyclic or heterocyclic. Preferred aryl groups include, for example, phenyl, benzyl, tolyl, xylyl, cumenyl, napthyl, biphenyl, thienyl, furyl, pyrrolyl, pyridinyl, pyrazinyl, thiazolyl, pyrimidinyl, quinolinyl, triazolyl, tetrazolyl, benzothiazolyl, benzofuryl, indolyl, indenyl, azulenyl, fluorenyl, anthracenyl, oxazolyl, isoxazolyl, isotriazolyl, imidazolyl, pyraxolyl, oxadiazolyl, indolizinyl, indolyl, isoindolyl, purinyl, quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, and the like. Aryls may be substituted or unsubstituted.

As used herein, "arylalkenyl" is an alkenyl radical substituted with an aryl group or an aryl radical substituted with an alkenyl group. Arylalkenyls may be substituted or unsubstituted.

As used herein, "arylalkyl" is an alkyl radical substituted with an aryl group or an aryl radical substituted with an alkyl group. Preferred arylalkyl groups include benzyl, phenylethyl, and phenylpropyl. Arylalkyls may be substituted or unsubstituted.

As used herein, "biohydrolyzable amides" are amides of the compounds of the present invention which do not interfere with the activity of the compound, or that are readily converted *in vivo* by a mammalian subject to yield an active compound.

As used herein, "biohydrolyzable esters" are esters of the compounds of the present invention which do not interfere with the activity of the compound, or that are readily converted *in vivo* by a mammalian subject to yield an active compound.

As used herein, "biohydrolyzable imides" are imides of the compounds of the present invention which do not interfere with the activity of the compound, or that are readily converted *in vivo* by a mammalian subject to yield an active compound.

As used herein, "carbocyclic ring", "carbocycle", or the like is a hydrocarbon ring radical. Carbocyclic rings are monocyclic or are fused, bridged, or spiro polycyclic rings. Unless otherwise specified, monocyclic rings contain from 3 to about 9 atoms, preferably from about 4 to about 7 atoms, and most preferably 5 or 6 atoms. Polycyclic rings contain from about 7 to about 17 atoms, preferably from about 7 to about 14 atoms, and most preferably 9 or 10 atoms. Carbocyclic rings (carbocycles) may be substituted or unsubstituted.

As used herein, "cycloalkyl" is a saturated carbocyclic or heterocyclic ring radical. Preferred cycloalkyl groups include, for example, cyclobutyl, cyclopentyl, and cyclohexyl. Cycloalkyls may be substituted or unsubstituted.

As used herein, "cycloalkenyl" is an unsaturated carbocyclic or heterocyclic ring radical having at least one double bond. Cycloalkenyls may be substituted or unsubstituted.

As used herein, preferred "halogens" (or "halos" or the like) are bromine, chlorine, iodine, and fluorine, more preferably, bromine, chlorine, and iodine, even more preferably bromine and chlorine, and most preferably chlorine.

As used herein, "heteroalkenyl" is an alkenyl radical comprised of carbon atoms and one or more heteroatoms wherein the heteroatoms are selected from the group consisting of oxygen, sulfur, nitrogen, and phosphorous, more preferably, oxygen, sulfur, and nitrogen. Heteroalkenyls may be substituted or unsubstituted.

As used herein, "heteroalkyl" is an alkyl radical comprised of carbon atoms and one or more heteroatoms wherein the heteroatoms are selected from the group consisting of oxygen,

sulfur, nitrogen, and phosphorous, more preferably, oxygen, sulfur, and nitrogen. Heteroalkyls may be substituted or unsubstituted.

As used herein, "heteroalkynyl" is an alkynyl radical comprised of carbon atoms and one or more heteroatoms wherein the heteroatoms are selected from the group consisting of oxygen, sulfur, nitrogen, and phosphorous, more preferably, oxygen, sulfur, and nitrogen. Heteroalkynyls may be substituted or unsubstituted.

As used herein, "heteroaryl" is an aryl radical comprised of carbon atoms and one or more heteroatoms wherein the heteroatoms are selected from the group consisting of oxygen, sulfur, nitrogen, and phosphorous, more preferably, oxygen, sulfur, and nitrogen. Heteroaryls may be substituted or unsubstituted.

As used herein, "heteroarylalkenyl" is an arylalkenyl radical wherein the aryl group and / or the alkenyl group is comprised of carbon atoms and one or more heteroatoms wherein the heteroatoms are selected from the group consisting of oxygen, sulfur, nitrogen, and phosphorous, more preferably, oxygen, sulfur, and nitrogen. Heteroarylalkenyls may be substituted or unsubstituted.

As used herein, "heteroarylalkyl" is an arylalkyl radical wherein the aryl group and / or the alkyl group is comprised of carbon atoms and one or more heteroatoms wherein the heteroatoms are selected from the group consisting of oxygen, sulfur, nitrogen, and phosphorous, more preferably, oxygen, sulfur, and nitrogen. Heteroarylalkyls may be substituted or unsubstituted.

As used herein, "heterocyclic ring", "heterocycle", or the like is a ring radical comprised of carbon atoms and one or more heteroatoms in the ring wherein the heteroatoms are selected from the group consisting of oxygen, sulfur, nitrogen, and phosphorous, more preferably, oxygen, sulfur, and nitrogen. Heterocycles are monocyclic or are fused, bridged, or spiro polycyclic rings. Unless otherwise specified, monocycles contain from 3 to about 9 atoms, preferably from about 4 to about 7 atoms, and most preferably 5 or 6 atoms. Polycycles contain from about 7 to about 17 atoms, preferably from about 7 to about 14 atoms, and most preferably 9 or 10 atoms. Heterocyclic rings (heterocycles) may be substituted or unsubstituted.

As used herein, "heterocycloalkyl" is a cycloalkyl having at least one heteroatom in the ring. Heterocycloalkyls may be substituted or unsubstituted.

As used herein, "heterocycloalkenyl" is a cycloalkenyl having at least one heteroatom in the ring. Heterocycloalkyls may be substituted or unsubstituted.

As used herein, a "lower" moiety (*e.g.*, "lower" alkyl) is moiety having 1 to about 6, preferably 1 to about 4, carbon atoms.

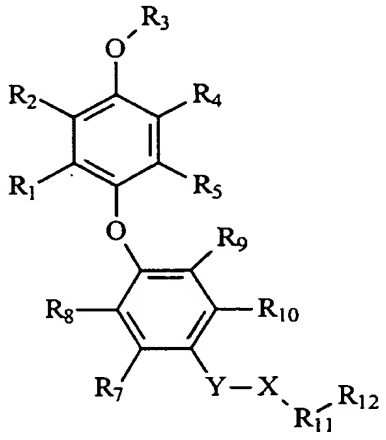
As used herein, "pharmaceutically acceptable" means suitable for use in a human or other mammal.

As used herein, "safe and effective amount of a compound" (or composition, or the like) means an amount that is effective to exhibit biological activity, preferably wherein the biological activity is arresting and / or reversing hair loss or promoting hair growth, at the site(s) of activity in a mammalian subject, without undue adverse side effects (such as toxicity, irritation, or allergic response), commensurate with a reasonable benefit / risk ratio when used in the manner of this invention.

As used herein unless otherwise specified, the term "substituted" in reference to a group, moiety, or the like, means having one or more substituent groups each independently selected from hydrogen, alkyl, alkenyl, alkoxy, hydroxy, nitro, amino, alkylamino, cyano, halo, thiol, aryl, cycloalkyl, heteroaryl, heterocycloalkyl (*e.g.*, piperidinyl, morpholinyl, pyrrolidinyl), imino, hydroxyalkyl, aryloxy, and arylalkyl, preferably hydrogen, alkyl, alkenyl, alkoxy, hydroxy, nitro, amino, alkylamino, halo, thiol, and aryloxy, more preferably hydrogen, alkyl, alkenyl, alkoxy, hydroxy, nitro, amino, alkylamino, and halo, even more preferably hydrogen, alkyl, and alkoxy, and most preferably alkoxy.

Compounds of the Present Invention

The compounds of the present invention have the structure:



and pharmaceutically acceptable salts, hydrates, and biohydrolyzable amides, esters, and imides thereof, wherein:

(a) R_1, R_2, R_5, R_7, and R_{10} are each, independently, selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl;

(b) R_4 is selected from the group consisting of halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, heteroarylalkyl, and heteroarylalkenyl; wherein when R_2 is hydrogen, Y is $-CH_2CHK_1$, X is selected from the group consisting of -NZ- and -NH-, and R_{12} is C_1 - C_4 alkyl, wherein K_1 is selected from hydrogen and C_1 - C_4 alkyl and Z is C_1 - C_4 alkyl, then R_4 is not arylalkyl;

(c) R_8 and R_9 are each, independently, selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, heteroarylalkyl, and heteroarylalkenyl; wherein at least one of R_8 and R_9 is not hydrogen;

(d) R_3 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, heteroarylalkyl and heteroarylalkenyl;

(e) Y is selected from the group consisting of bond, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl;

(f) X is selected from the group consisting of -NZ-, -NH-, and -O-;

(g) R_{11} is selected from the group consisting of bond and -C(O)-; wherein when Y is bond and X is -O- then R_{11} is -C(O)-; and wherein when Y is alkyl and X is -O- then R_{11} is not -C(O)-;

(h) R_{12} is selected from the group consisting of alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, and heteroarylalkenyl; or wherein when R_{11} is bond, then R_{12} and Z may be optionally bonded together to form a cycle selected from the group consisting of cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl; wherein when R_{12} is heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, heteroarylalkyl, or heteroarylalkenyl, then a heteroatom of R_{12} is not directly covalently bonded to R_{11}; wherein when Y is bond or hydroxy-substituted ethyl, X is -NH-, and R_{11} is bond, then R_{12} is not methyl; and wherein when Y is bond, X is -O-, and R_{11} is -C(O)- then R_{12} is not aryl; and

(i) Z is selected from the group consisting of alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl; or wherein when R_{11} is bond, then R_{12} and Z may be optionally bonded together to form a cycle selected from the group consisting of cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl.

The present compounds are substituted biphenyl ether compounds. The substituents are described in further detail below.

The Substituents R_1, R_2, R_5, R_7, and R_{10}

The substituents R_1, R_2, R_5, R_7, and R_{10} each substitute on one of the phenyl rings of the structure shown herein. R_1, R_2, R_5, R_7, and R_{10} are each, independently, selected from hydrogen, halogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl.

R_1, R_2, R_5, R_7, and R_{10} are preferably each, independently, selected from hydrogen, halogen, alkyl, alkenyl, heteroalkyl, and heteroalkenyl. R_1, R_2, R_5, R_7, and R_{10} are more preferably each, independently, selected from hydrogen, halogen, and lower alkyl. Most preferably, R_1, R_2, R_5, R_7, and R_{10} are each hydrogen.

The Substituent R_4

The substituent R_4 is selected from halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, heteroarylalkyl, and heteroarylalkenyl; wherein when R_2 is hydrogen, Y is $-CH_2CHK_1$, X is selected from the group consisting of -NZ- and -NH-, and R_{12} is C_1 - C_4 alkyl, wherein K_1 is selected from hydrogen and C_1 - C_4 alkyl and Z is C_1 - C_4 alkyl, then R_4 is not arylalkyl.

R_4 is preferably selected from halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, heteroarylalkyl, and heteroarylalkenyl. R_4 is more preferably selected from halogen, alkyl, alkenyl, heteroalkyl, and heteroalkenyl. R_4 is even more preferably selected from halogen, alkyl, alkenyl, and heteroalkyl. R_4 is most preferably selected from halogen and lower alkyl. The most preferred halogens for R_4 are chlorine, bromine, and iodine, preferably chlorine and iodine, and most preferably iodine. The most preferred lower alkyls for R_4 are methyl, ethyl, *iso*-propyl, and *tert*-butyl, preferably methyl, *iso*-propyl, and *tert*-butyl, more preferably *iso*-propyl or *tert*-butyl. Most preferably, R_4 is lower alkyl, particularly *iso*-propyl or *tert*-butyl.

The Substituents R_8 and R_9

R_8 and R_9 are each, independently, selected from hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, heteroarylalkyl, and heteroarylalkenyl; wherein at least one of R_8 and R_9 is not hydrogen. Preferably, each of R_8 and R_9 are not hydrogen.

R_8 and R_9 are preferably each, independently, selected from halogen, alkyl, alkenyl, heteroalkyl, and heteroalkenyl. R_8 and R_9 are more preferably each, independently, selected from halogen, alkyl, alkenyl, and heteroalkyl. R_8 and R_9 are even more preferably each, independently, selected from halogen and lower alkyl. The most preferred halogens for R_8 and R_9 are chlorine and bromine, preferably chlorine. The most preferred lower alkyls for R_8 and R_9 are methyl, ethyl, *iso*-propyl, and *tert*-butyl, preferably methyl, *iso*-propyl, and *tert*-butyl, more preferably methyl and *iso*-propyl. Most preferably, R_8 and R_9 are each, independently, selected from lower alkyl and halogen, particularly methyl and chlorine, respectively.

The Substituent R_3

R_3 substitutes on the oxygen moiety of the biphenyl structure as shown above. R_3 is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, heteroarylalkyl and heteroarylalkenyl. Preferably, R_3 is selected from hydrogen, alkyl, alkenyl, cycloalkyl, aryl, arylalkyl, heteroalkyl, heteroalkenyl, heterocycloalkyl, heteroaryl, and heteroarylalkyl. More preferably, R_3 is selected from hydrogen, alkyl, alkenyl, aryl, arylalkyl, heteroalkyl, heteroaryl, and heteroarylalkyl. Still more preferably, R_3 is selected from hydrogen, alkyl, alkenyl, arylalkyl (preferably benzyl), heteroalkyl, and heteroarylalkyl. Even more preferably, R_3 is selected from hydrogen, lower alkyl, and lower alkenyl. Most preferably, R_3 is selected from hydrogen and lower alkyl. The most preferred lower alkyl for R_3 is methyl.

The Substituent Y

Y is selected from bond, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl. Wherein Y is bond, X is directly bonded to the phenyl ring bearing R_7, R_8, R_9, and R_{10}. Y is preferably selected from bond, alkyl, alkenyl, heteroalkyl, and heteroalkenyl. More preferably, Y is selected from bond and lower alkyl. Most preferably, Y is bond.

The Substituent X

X is selected from -NZ-, -NH-, and -O-. Z substitutes on the nitrogen of -NZ- and is selected from alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl; or wherein when R_{11} is bond, then R_{12} and Z may be optionally bonded together to form a cycle selected from cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl. Preferably, Z is selected from alkyl, alkenyl, heteroalkyl, and heteroalkenyl, or R_{12} and Z are bonded together to form a cycle selected from cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl. More preferably, Z is lower alkyl, or R_{12} and Z are bonded together to form a cycle selected cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl. Most preferably, Z is C_1 - C_3 alkyl, particularly methyl, or R_{12} and Z are bonded together to form a cycle selected from cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl.

Preferably, X is selected from -NH- and -NZ-. Most preferably, X is -NH-, -N(CH_3)-, or -NZ- wherein R_{12} and Z are bonded together to form a cycle selected from cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl.

Wherein R_{12} is bonded to Z to form a cycle, the cycle is preferably selected from cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, more preferably from cycloalkyl, heterocycloalkyl, and aryl, even more preferably from cycloalkyl and heterocycloalkyl, and most preferably heterocycloalkyl. In addition to the optional substituents described herein above, the cycle may also optionally bear one or more oxo (*i.e.*, doubly bonded oxygen) substituents. Non-limiting examples of these cycles include piperidinyl, morpholinyl, piperazinyl, pyrrolidinyl, indolinyl, succinimidyl, and hydantoinyl.

The Substituent R_{11}

R_{11} is selected from bond and -C(O)-. However, wherein when Y is bond and X is -O- then R_{11} is -C(O)-; and wherein Y is alkyl and X is -O- then R_{11} is not -C(O)- (but rather is bond).

Wherein X is selected from -NZ- and -NH-, then both bond and -C(O)- are highly preferred for R_{11}, but most preferably, R_{11} is -C(O)-. Wherein X is -O-, R_{11} is most preferably -C(O)-.

The Substituent R_{12}

R_{12} is selected from alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, and heteroarylalkenyl; or wherein when R_{11} is bond, then R_{12} and Z may be

optionally bonded together to form a cycle selected from the group consisting of cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl; wherein when R_{12} is heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, heteroarylalkyl, or heteroarylalkenyl, then a heteroatom of R_{12} is not directly covalently bonded to R_{11}. Accordingly, carbamates and ureas at the -Y-X-R_{11}-R_{12} linkage are not contemplated within the present invention. For example, wherein R_{12} is heteroalkyl, it is not, *e.g.*, -O-CH_2-CH_3, but could be, *e.g.*, -CH_2-O-CH_3.

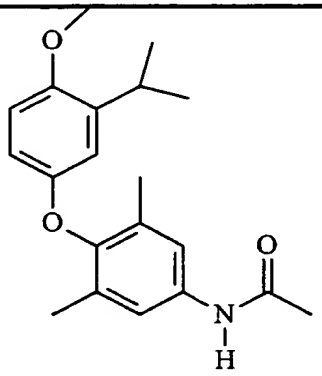
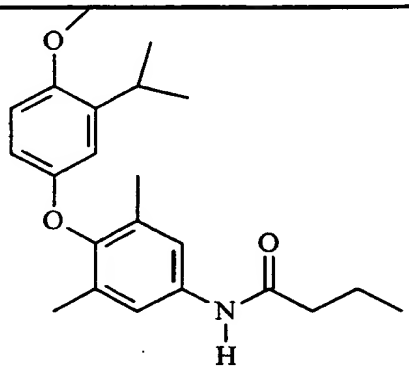
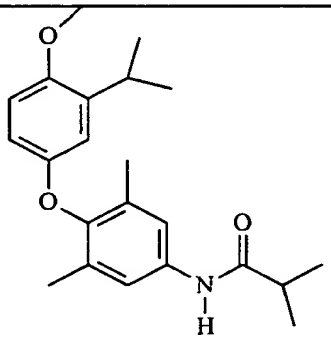
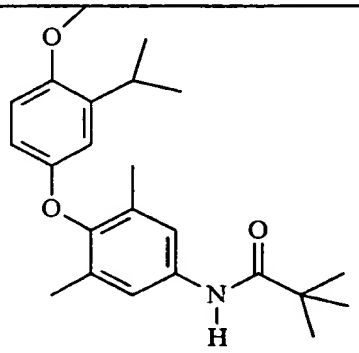
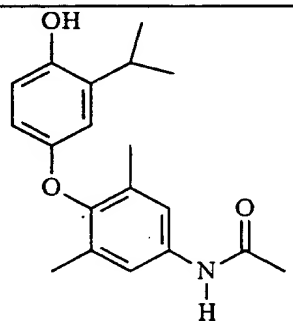
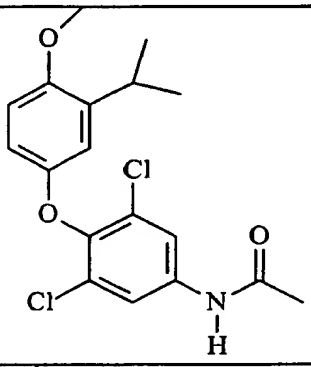
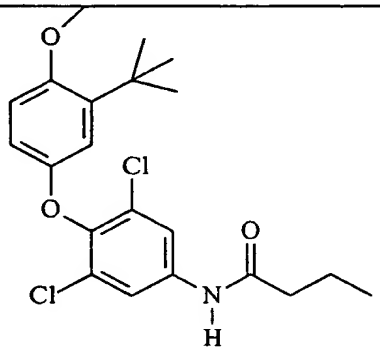
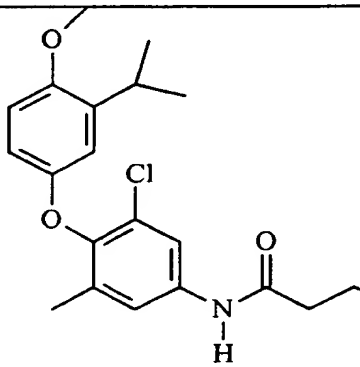
Furthermore, wherein Y is bond or hydroxy-substituted ethyl (*i.e.*, -$CHOHCH_2$-), X is -NH-, and R_{11} is bond, then R_{12} is not methyl. More preferably, wherein Y is bond or alkyl, X is -NH-, and R_{11} is bond, then R_{12} is not methyl. Also, wherein Y is bond, X is -O-, and R_{11} is -C(O)- then R_{12} is not aryl.

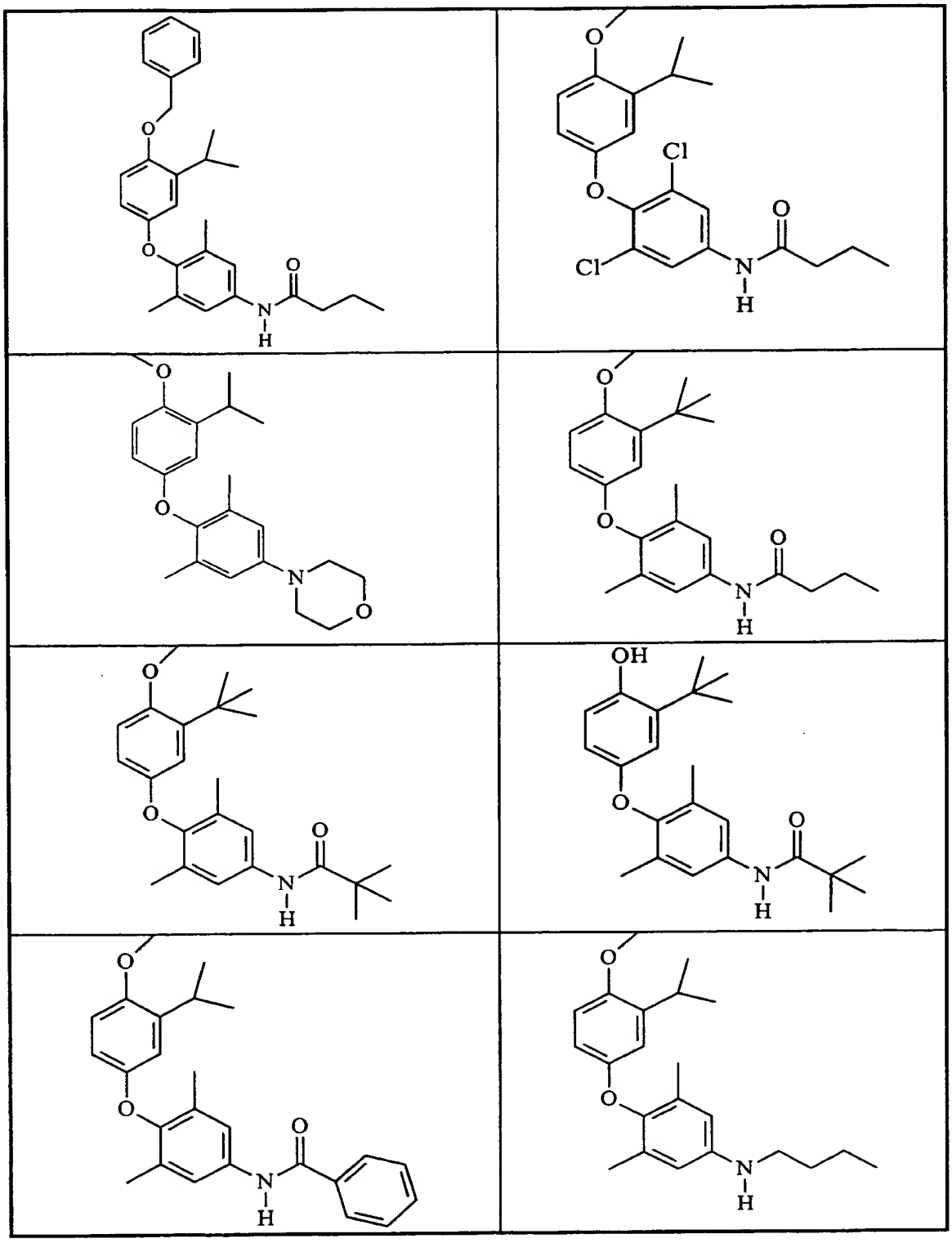
Preferably, R_{12} is selected from alkyl, alkenyl, heteroalkyl, heteroalkenyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, and heteroarylalkenyl, or is bonded to Z to form a cycle selected from cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl. More preferably, R_{12} is selected from alkyl, alkenyl, heteroalkyl, heteroalkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, and heteroarylalkenyl, or is bonded to Z to form a cycle selected from cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl. Even more preferably, R_{12} is selected from alkyl, heteroalkyl, arylalkyl, and heteroarylalkyl, or is bonded to Z to form a cycle selected from cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl. Most preferably, R_{12} is lower alkyl, or is bonded to Z to form a cycle selected from cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl. The most preferred lower alkyls for R_{12} are methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *tert*-butyl, and *n*-pentyl, particularly methyl, *n*-propyl, *iso*-propyl, *n*-butyl, and *tert*-butyl.

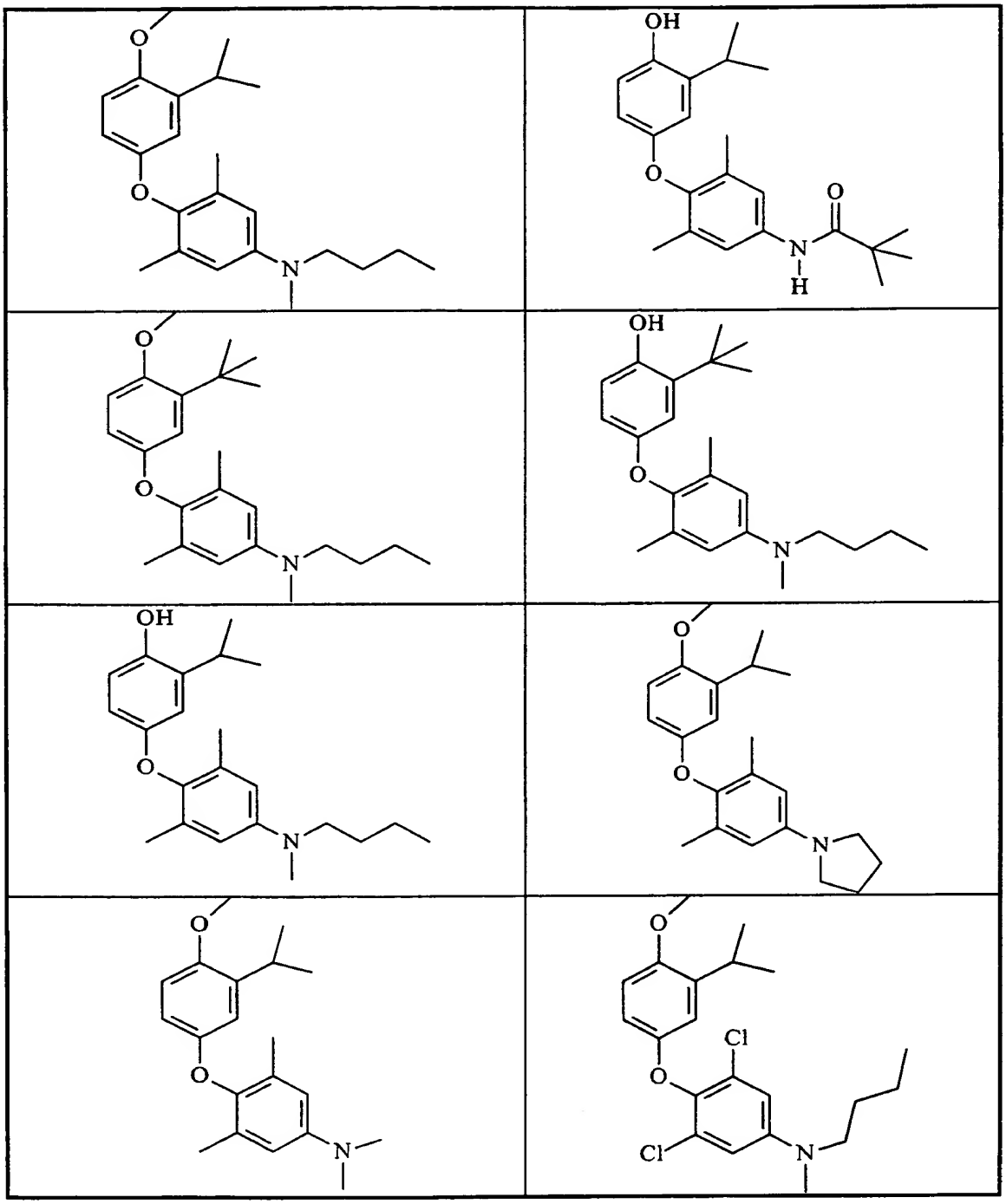
Wherein R_{12} is bonded to Z to form a cycle, the cycle is preferably selected from cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, more preferably from cycloalkyl, heterocycloalkyl, and aryl, even more preferably from cycloalkyl and heterocycloalkyl, and most preferably heterocycloalkyl. In addition to the optional substituents described herein above, the cycle may also optionally bear one or more oxo (*i.e.*, doubly bonded oxygen) substituents. Non-limiting examples of these cycles include piperidinyl, morpholinyl, piperazinyl, pyrrolidinyl, indolinyl, succinimidyl, and hydantoinyl.

Preferred compounds of the present invention are set forth in the following tables:

Table 1 - Preferred Compounds of the Present Invention





Analytical Methods

The present invention relates to compounds and methods for treating hair loss. Preferably, the compound utilized in the present invention will be cardiac-sparing. Compounds (test compounds) may be tested for their ability to induce anagen and their lack of cardiotoxicity (cardiac-sparing) using the following methods. Alternatively, other methods well-known in the

art may be used (but with the term "cardiac-sparing" being defined according to the method disclosed herein below).

Cardiotoxicity Assay:

The cardiotoxicity assay measures the potential of a test compound to adversely affect the cardiovascular system. As thyroid hormone (T3) damages the cardiovascular system, the heart enlarges. See, e.g., Gomberg-Maitland et al., "Thyroid hormone and Cardiovascular Disease", *American Heart Journal*, Vol. 135(2), pp. 187-196 (1998); Klein and Ojamaa, "Thyroid Hormone and the Cardiovascular System", *Current Opinion in Endocrinology and Diabetes*, Vol. 4, pp.341-346 (1997); and Klemperer et al., "Thyroid Hormone Therapy and Cardiovascular Disease", *Progress in Cardiovascular Diseases*, Vol. 37 (4), pp. 329-336 (1996). This increases the weight of the heart relative to whole body weight. The cardiotoxicity assay herein below is used to test compounds for potentially adverse cardiac effects by measuring their effect on the heart-to-body weight ratio.

Two groups each of six male Sprague Dawley rats (Harlan Sprague Dawley, Inc., Indianapolis, IN) (each weighing from approximately 220 grams to 235 grams) are utilized. The first group is a vehicle control group and the second group is a test compound group. The length of the assay is 30 days, with treatment of vehicle or test compound in vehicle daily for 28 of those days as described below.

Prior to initiation of the assay, each rat is allowed to acclimate to standard environmental conditions for 5 days. Each rat receives food (standard rat chow diet) and water *ad libitum* 5 days prior to initiation of the assay as well as to termination of the study.

The vehicle is 91:9 (v:v) propylene glycol:ethanol. The test compound is prepared at a concentration of 500 μg/mL in the vehicle.

Each rat is weighed on day 1 of the assay. Dosage calculations are then performed: each rat will be administered daily a dosing solution of vehicle or test compound in vehicle (depending on whether the rat is in the vehicle control group or the test compound group, respectively) at 500 μL of dosing solution per kg of rat. For rats in the test compound group, this corresponds to a dose of 250 μg of test compound per kg of rat.

Day 2 is the first day of treatment with dosing solution for both groups. Body weights are taken for each rat on days 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, 26, and 29 prior to dosing for that day; for each rat, the dosing solutions are recalculated and administered accordingly upon change in body weight.

Treatment occurs once daily in the morning on days 2 through 29, inclusive, for each rat in each group. For each treatment, the dosing solution is administered subcutaneously between the shoulders of the rat such that the injection sites are rotated in this area.

On day 30 in the morning, the rats of each group are euthanized with CO_2 from dry ice. Each rat is immediately weighed for total body weight.

The hearts of each rat are then excised as follows. An incision is made to expose the abdominal cavity. The rib cage is carefully cut at the sternum with small scissors, such that the heart and lungs are exposed. With small scissors and forceps, the vessels connected to the heart are cut away from the heart. These vessels include the caudal vena cava, left cranial vena cava (pulmonary trunk), right cranial vena cava, thoracic aorta, right subclavian artery, internal thoracic artery and vein, and any other small attachments. The heart is then immediately taken out intact, including the left and right auricles and left and right ventricles. Immediately thereafter, any excess tissue is trimmed away, the heart is lightly blotted on a paper towel until no more blood is visibly left behind on the paper towel, and the heart is weighed.

The heart weight is divided by the body weight after euthanization for each rat to give the heart/body ratio. The heart/body ratios for each rat in the vehicle control group are added together and divided by 6 (*i.e.*, the total number of rats in the group) to give RV (ratio for vehicle control group). Similarly, the heart/body ratios for each rat in the test compound group are added together and divided by 6 to give RT (ratio for test compound group).

The index C is then calculated by dividing RT by RV. As defined herein, where C is less than 1.3, the test compound is cardiac-sparing. Preferably, C is less than 1.2, more preferably less than 1.15, and most preferably less than 1.1. In accordance with this method, T3 and T4 are not cardiac-sparine.

Telogen Conversion Assay:

The Telogen Conversion Assay measures the potential of a test compound to convert mice in the resting stage of the hair growth cycle ("telogen"), to the growth stage of the hair growth cycle ("anagen").

Without intending to be limited by theory, there are three principal phases of the hair growth cycle: anagen, catagen, and telogen. It is believed that there is a longer telogen period in C3H mice (Harlan Sprague Dawley, Inc., Indianapolis, IN) from approximately 40 days of age until about 75 days of age, when hair growth is synchronized. It is believed that after 75 days of age, hair growth is no longer synchronized. Wherein about 40 day-old mice with dark fur (brown or black) are used in hair growth experiments, melanogenesis occurs along with hair

(fur) growth wherein the topical application of hair growth inducers are evaluated. The Telogen Conversion Assay herein below is used to screen compounds for potential hair growth by measuring melanogenesis.

Three groups of 44 day-old C3H mice are utilized: a vehicle control group and a test compound group, wherein the test compound group is administered a compound according to the present invention. The length of the assay is at least 19 days with 15 treatment days (wherein the treatment days occur Mondays through Fridays). Day 1 is the first day of treatment. Most studies will end on Day 19, but a few may be carried out to Day 24 if the melanogenesis response looks positive, but occurs slowly. A typical study design is shown in Table 2 below. Typical dosage concentrations are set forth in Table 2, however the ordinarily skilled artisan will readily understand that such concentrations may be modified.

Table 2

Group #	Animal #	Compound	Concentration	Application volume	Length of Study
1	1 - 10	Test Compound	0.1% in vehicle**	400 µL topical	19 or 24 days
2	11 - 20	Positive Control (T3)	0.01% in vehicle**	400 µL topical	19 or 24 days
3	21 - 30	Vehicle**	N/A	400 µL topical	19 or 24 days

**The vehicle is 60% ethanol, 20% propylene glycol, and 20% dimethyl isosorbide (commercially available from Sigma Chemical Co., St. Louis, MO).

The mice are treated topically Monday through Friday on their lower back (base of tail to the lower rib). A pipettor and tip are used to deliver 400 µL to each mouse's back. The 400 µL application is applied slowly while moving hair on the mouse to allow the application to reach the skin.

While each treatment is being applied to the mouse topically, a visual grade of from 0 to 4 will be given to the skin color in the application area of each animal. As a mouse converts from telogen to anagen, its skin color will become more bluish-black. As indicated in Table 3, the grades 0 to 4 represent the following visual observations as the skin progresses from white to bluish-black.

Table 3

Visual Observation	Grade
Whitish Skin Color	0
Skin is light gray (indication of initiation of anagen)	1
Appearance of Blue Spots	2
Blue Spots are aggregating to form one large blue area	3
Skin is dark blue (almost black) with color covering majority of treatment area (indication of mouse in full anagen)	4

Methods of Making

The compounds of the present invention are prepared according to methods which are well-known to those ordinarily skilled in the art. The starting materials used in preparing the compounds of the invention are known, made by known methods, or are commercially available as a starting material.

It is recognized that the ordinarily skilled artisan in the art of organic chemistry can readily carry out standard manipulations of organic compounds without further direction. Examples of such manipulations are discussed in standard texts such as J. March, Advanced Organic Chemistry, John Wiley & Sons, 1992.

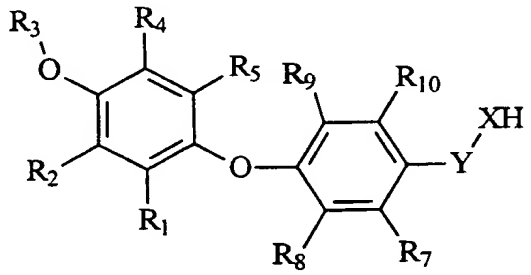
The ordinarily skilled artisan will readily appreciate that certain reactions are best carried out when other functionalities are masked or protected in the compound, thus increasing the yield of the reaction and / or avoiding any undesirable side reactions. Often, the ordinarily skilled artisan utilizes protecting groups to accomplish such increased yields or to avoid the undesired reactions. These reactions are found in the literature and are also well within the scope of the ordinarily skilled artisan. Examples of many such manipulations can be found in, for example, T. Greene, Protecting Groups in Organic Synthesis, John Wiley & Sons, 1981.

The compounds of the present invention may have one or more chiral center. As a result, one may selectively prepare one optical isomer, including diastereomers and enantiomers, over another, for example by chiral starting materials, catalysts or solvents, or may prepare both stereoisomers or both optical isomers, including diastereomers and enantiomers at once (a racemic mixture). Since the compounds of the invention may exist as racemic mixtures, mixtures of optical isomers, including diastereomers and enantiomers, or stereoisomers may be separated using known methods, such as through the use of, for example, chiral salts and chiral chromatography.

In addition, it is recognized that one optical isomer, including a diastereomer and enantiomer, or a stereoisomer, may have favorable properties over the other. Thus, when disclosing and claiming the invention, when one racemic mixture is disclosed, it is clearly contemplated that both optical isomers, including diastereomers and enantiomers, or stereoisomers substantially free of the other are disclosed and claimed as well.

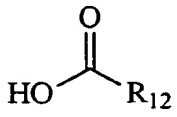
The compounds of the present invention may be prepared using a variety of procedures known to those ordinarily skilled in the art. Non-limiting general preparations include the following.

The compounds of the invention may be prepared, after removal of temporary protection groups (see, e.g., T. Greene, Protecting Groups in Organic Synthesis, John Wiley & Sons, 1981), by condensing (*e.g.*, acylating or alkylating) a compound of the structure:

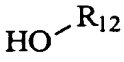


(I)

wherein R_1, R_2, R_3, R_4, R_5, R_7, R_8, R_9, R_{10}, Y and X are defined herein above and are in an appropriately protected form if necessary, with a reactive derivative of the structure:

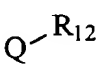


(II)



(III)

or



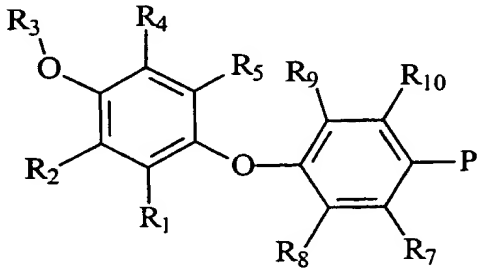
(IV)

wherein R_{12} is defined herein above and is in an appropriately protected form if necessary and Q is halogen, preferably bromine or iodine, and most preferably iodine. Reactive derivatives of structure II include activated esters such as, for example, 1-hydroxybenzotriazole esters, mixed

anhydrides with organic or inorganic acids such as hydrochloric acid and sulfonic acids, and symmetrical anhydrides of the acids of structure II. Activated derivatives of structure III include trifluromethane sulfonyl esters and other activated derivatives known to those ordinarily skilled in the art. Compounds of structure IV are generally appropriately reactive without further modification; however, it may be necessary to convert a less reactive halogen to a more reactive halogen such as bromine or iodine as is known by those ordinarily skilled in the art. Many appropriately activated derivatives of structures II, III, or IV are commercially available and others may be prepared by methods known to those ordinarily skilled in the art. Non-limiting examples of condensations of this type are provided in Examples 2, 3, 4, 8, 9, 10, 12, 13, 14, 16, 18, 19 herein and an example of the removal of a temporary protecting group is provided in Example 17.

Additionally, appropriately protected compounds resulting from the condensation of a compound of structure I with a compound of structure II, III, or IV may be further modified to afford additional compounds of the invention after removal of temporary protection groups. These modifications include, but are not limited to, reduction of an amide to an amine as described in Examples 7b and 15 to afford a secondary or tertiary amine, alkylation of an amide as described in Example 7a and alkylation of the aromatic rings using Friedel-Crafts conditions similar to those described in Example 10b.

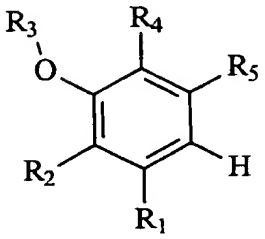
Compounds of structure I may be prepared from a biaryl ether intermediate of structure V wherein P is an electron-withdrawing functionality, for example, a nitro, cyano or acyl group.



(V)

Compounds of structure V can be prepared by conversion of an anisole of structure VI to a symmetrical bis-aryl iodonium salt as in Example 1b herein followed by condensation in a copper catalyzed reaction with a phenol of structure VI. Appropriately substituted anisoles of structure VI are commercially available or may be prepared from their corresponding phenols as described, for example, in Example 1a herein, or may be synthesized using methods known to those ordinarily skilled in the art. Appropriately substituted phenols of structure VII are

commercially available or may be prepared using methods known to those ordinarily skilled in the art



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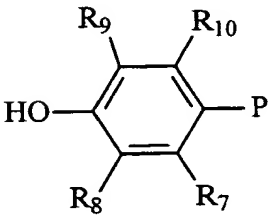
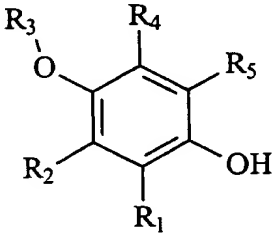
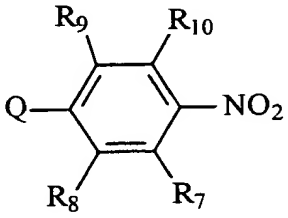


(VII)

Alternatively, compounds of structure V may be prepared by condensing a 4-halonitrobenzene of structure IX with an appropriately substituted phenol of structure VIII in a base catalyzed reaction as described in Examples 2a, 10a, and 11a herein.



(VIII)



(IX)

Compounds of structure V may be further modified wherein R_2 and / or R_4 is hydrogen by acylation under Friedel-Crafts conditions as described in Example 10c.

Compounds of the structure V can be converted to compounds of the structure I by further transformation. For example, wherein P is nitro, the resulting compound of structure V

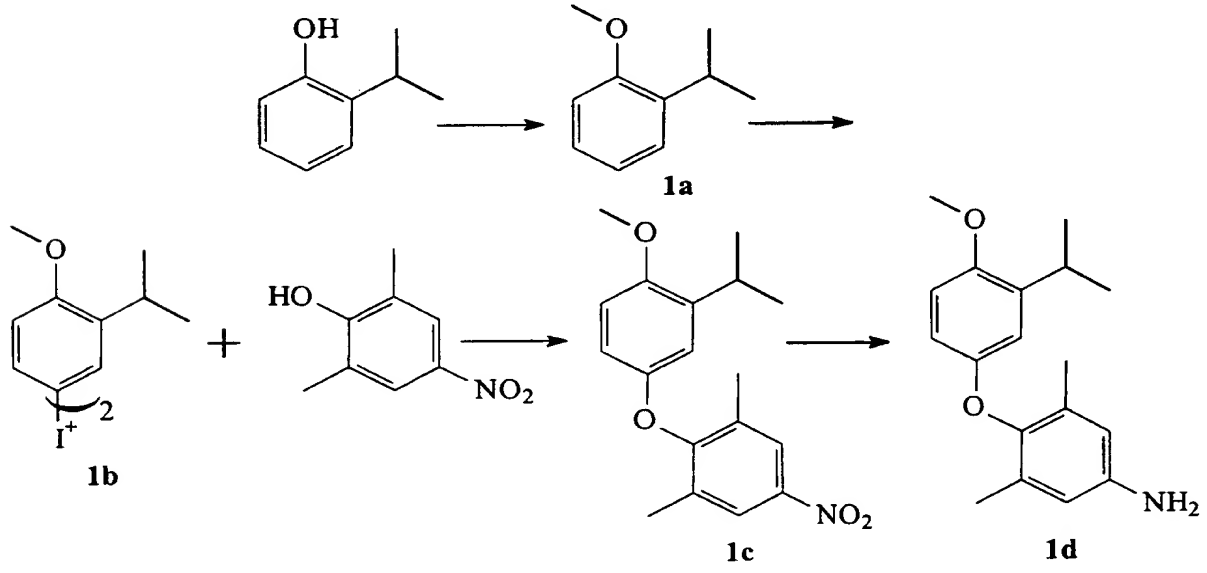
can be converted into a compound of structure I by reduction to the amine using standard chemical reactions utilizing, for example, palladium on carbon or tin chloride. Wherein P is acyl, such compounds may be converted to compounds of structure I using, for example, peracetic acid to convert the acetophenone to an acetyl ester. Alternatively, the compounds of structure I may be prepared by reductive alkylation of the ketone using a primary or secondary amine and a borohydride reducing reagent. Wherein P is cyano, such compounds may be converted a compound of structure I by reduction to an alkylamino compound using conditions known to those ordinarily skilled in the art.

For even further guidance, the following non-limiting examples illustrate more specifically the methods of making various compounds of the present invention.

As used herein, the following abbreviations are used:

Trifluoroacetic acid	TFA
Tetrahydrofuran	THF
N,N-dimethylformamide	DMF
N,N - diisopropylethylamine	i-Pr_2NEt or i-Pr_2EtN
N-*tert*-butoxycarbonyl	BOC

Example 1



1a. 2-*iso*-propyl anisole: Potassium hydroxide (5.6 g) is added to 13.4 mL acetone followed by 2-*iso*-propylphenol (13.6 g). After the potassium hydroxide is dissolved, methyl iodide (14.2 g) is added. The reaction is refluxed overnight. 150 mL of water is added. This reaction is extracted 3 times with 100 mL diethyl ether. The organic layer is extracted twice with 100 mL

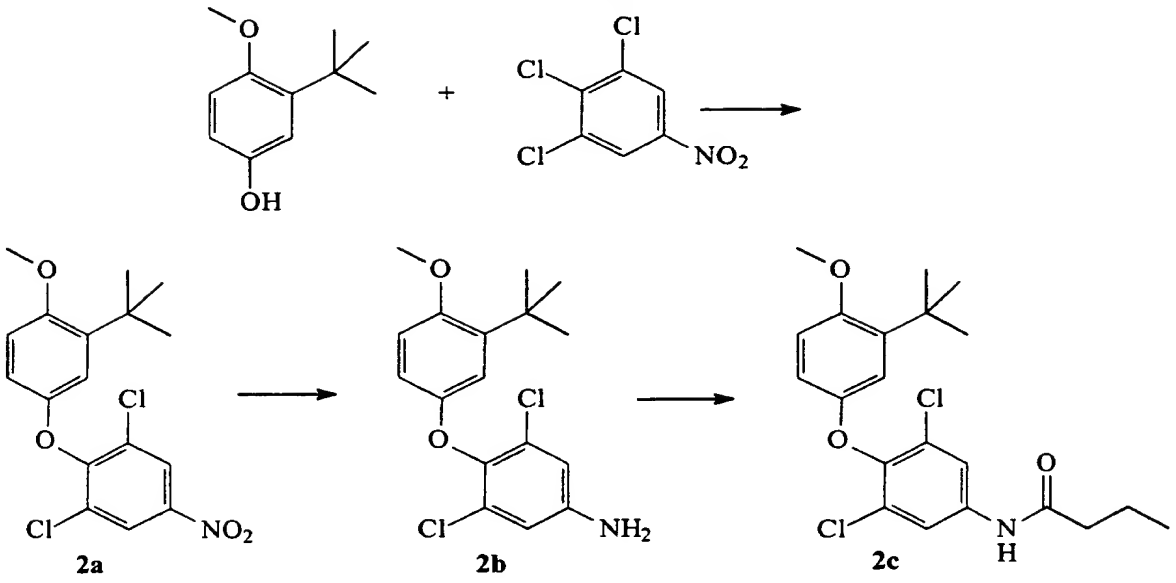
10% sodium hydroxide in water, once with 100 mL water, and once with 100 mL saturated ammonium chloride. After drying over magnesium sulfate, the organic solution is dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The material is fractionally distilled under reduced pressure to afford **1a**.

1b. Bis(3-*iso*-propyl-4-methoxyphenyl)iodonium Tetrafluoroborate: Acetic Anhydride, 7 mL, is cooled to -15 ^{0}C in a dry ice acetone bath. Fuming nitric (5.4 mL) is added dropwise. Iodine (2.5 g) is added in one piece followed by dropwise addition of TFA (4.7 mL). After 20 minutes, the reaction is removed from the bath and stirred at room temperature for 30 minutes. After the iodine has dissolved, the reaction is sparged to remove nitrogen oxides and then concentrated under vacuum. The material is then taken up in 15 mL acetic anhydride and cooled to -10 ^{0}C. To this cooled solution is added dropwise a solution of 2-*iso*-propyl anisole (**1a**; 7.43 g) in 35 mL acetic anhydride and 5 mL TFA. The reaction is allowed to stand in the refrigerator overnight. After allowing the reaction to return to room temperature for 3 hours, the reaction is concentrated under high vacuum. The residue is taken up in 25 mL methanol, 25 mL 10% sodium bisulfite, and 188 mL 2M sodium tetrafluoroborate. The mixture is stirred vigorously for 30 minutes and the supernatant is decanted off. To the residue is added 200 mL hexane and it is stirred for an additional 30 minutes. At that time, the solid is collected, washed with hexane, and dried under vacuum to afford **1b**.

1c. 2',6'-dimethyl-3-*iso*-propyl-4-methoxy-4'-nitrodiphenyl ether: Bis(3-*iso*-propyl-4-methoxyphenyl)iodonium tetrafluoroborate (**1b**, 3 g), is weighed is taken up in 7.7 mL dichloromethane and 0.5g copper bronze is added. The mixture is cooled in an ice water bath. A solution of 2,6-dimethyl-4-nitrophenol (0.65 g) and triethylamine (0.44 g), in 5.2 mL dichloromethane is added dropwise. The reaction is placed in the dark and stirred for 5 days. At this time, the reaction is filtered through celite and concentrated under reduced pressure. Purification of the product by chromatography over silica gel followed by crystallization from hexane:ethyl acetate affords **1c**.

1d. 2',6'-dimethyl-3-*iso*-propyl-4-methoxy-4'-aminodiphenyl ether: 2',6'-dimethyl-3-*iso*-propyl-4-methoxy-4'-nitrodiphenyl ether (**1c**, 5.25 g), is dissolved in 50 mL ethanol and 7.5 mL ethyl acetate and 0.75 mg of 10% palladium on carbon is added. The reaction is hydrogenated for 3 hours, then filtered through Celite and concentrated under reduced pressure to provide the desire amine **1d**.

Example 2



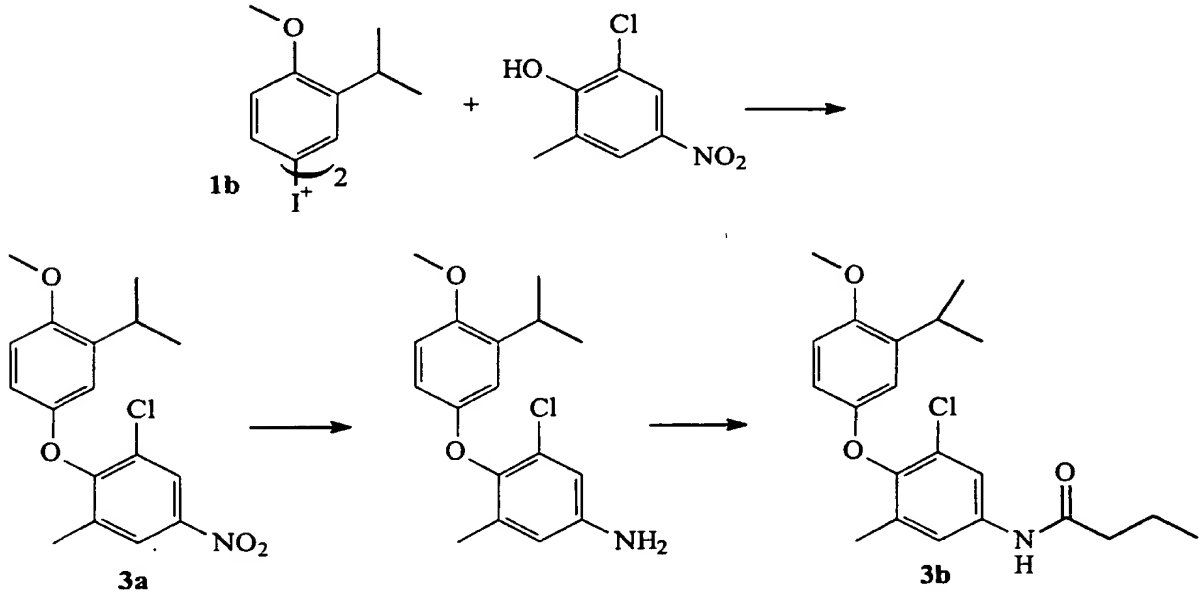
2a. 2', 6'-dichloro-3-*tert*-butyl-4-methoxy-4'-nitrodiphenyl ether: Potassium carbonate (67.5 g) is suspended in 1 liter of methylsulfoxide. 1,2,3-trichloro-5-nitrobenzene (99 g), is added followed by 2-*tert*-butyl-4-hydroxyanisole (80 g). The reaction is heated *via* a heating mantle set at 80 °C and stirred with a mechanical stirrer for 20 hours. The reaction is allowed to cool to 40 °C and 2 liters of cold water is added while stirring. After stirring for 2 hours the reaction mixture is filtered through a medium porosity frit and the filter cake is allowed to air dry for 17 hours followed drying by vacuum pump for 4 hours to afford **2a**.

2b. 3,5-dichloro-4-(4'-methoxy-3'-*tert*-butylphenoxy)benzylamine: 2',6'-dichloro-3-*tert*-butyl-4-methoxy-4'-nitrodiphenyl ether (**2a**, 0.35 g), is dissolved in 5 mL of 49:1 ethanol:ethyl acetate by heating on a water bath (40 °C) and to this solution, tin chloride dihydrate (1.1 g) is added. The reaction is heated to 70 °C and stirred for 1.5 hours. The reaction is allowed to cool to room temperature, then poured onto ice. The pH is made slightly basic (pH about 7 - 8) by addition of 5% aqueous sodium bicarbonate (50 mL) and then extracted with ethyl acetate (50 mL). The organic phase is washed with brine (50 mL), treated with charcoal and dried over $MgSO_4$ and filtered. The filtrate is evaporated to provide **2b**.

2c. *N*-[3,5-dichloro-4-(4'-methoxy-3'-*tert*-butylphenoxy)phenyl]butyramide: 3,5-dichloro-4-(4'-methoxy-3'-*tert*-butylphenoxy)benzylamine (**2b**, 0.24 g), is suspended in pyridine (0.12

mL), and butyric anhydride (0.23 mL) is added. The reaction is allowed to proceed for two hours and then it is concentrated under reduced pressure. The resulting residue is presorbed onto silica gel using acetone and purified by chromatography on silica gel. The product is crystallized from hexanes to afford **2c**.

Example 3

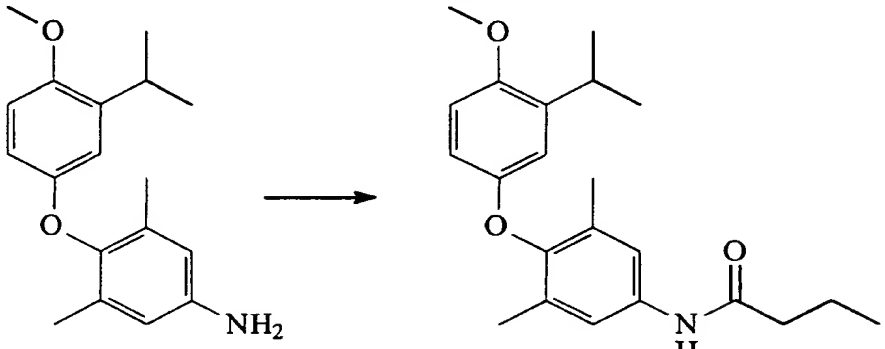


3a. 2'-chloro-4'-nitro-6'-methyl-3-*iso*-propyl-4-methoxydiphenyl ether: Bis(3-*iso*-propyl-4-methoxyphenyl)iodonium tetrafluoroborate (**1b**, 1.5 g), is taken up in 5 mL dichloromethane. Copper bronze (0.26 g) is added. The mixture is cooled in an ice water bath. A solution of 2-chloro-4-nitro-6 methylphenol (0.37 g) and triethylamine (0.43 g), in 5 mL dichloromethane is added dropwise. The reaction is placed in the dark and stirred for 5 days. At this time, the reaction is filtered through celite and concentrated under reduced pressure. Purification of the product by chromatography on silica gel affords **3a**.

3b. *N*-[3-chloro-5-methyl-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenyl]butyramide: 2'-chloro-4'-nitro-6'-methyl-3-*iso*-propyl-4-methoxydiphenyl ether (**3a**, 200 mg) is dissolved in 15 mL ethanol and 30 mg of 10% palladium on carbon is added. The reaction is hydrogenated for 3 hours, then filtered through Celite and concentrated under reduced pressure. Butyric anhydride (4 mL), is added to the residue and the reaction is stirred overnight. At this time, 20 mL water and 20 mL ethyl acetate are added and the reaction mixture is extracted with 1 N NaOH until the pH of the aqueous layer is above 10. After extracting once with brine, drying over magnesium

sulfate and filtering, the organic layer is concentrated under reduced pressure and purified by chromatography on silica gel to afford **3b**.

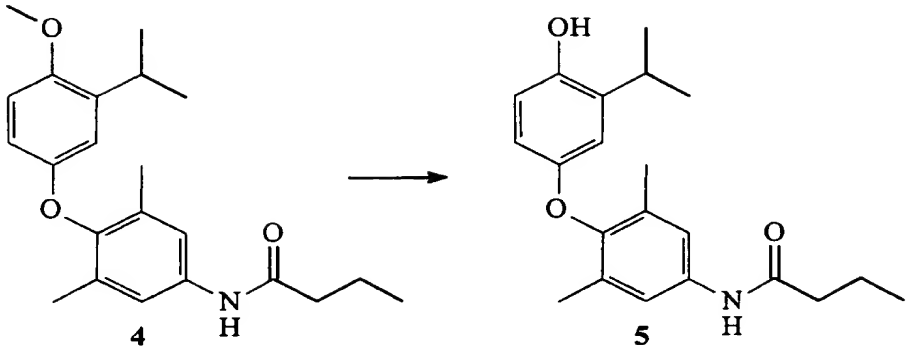
Example 4



1d **4**

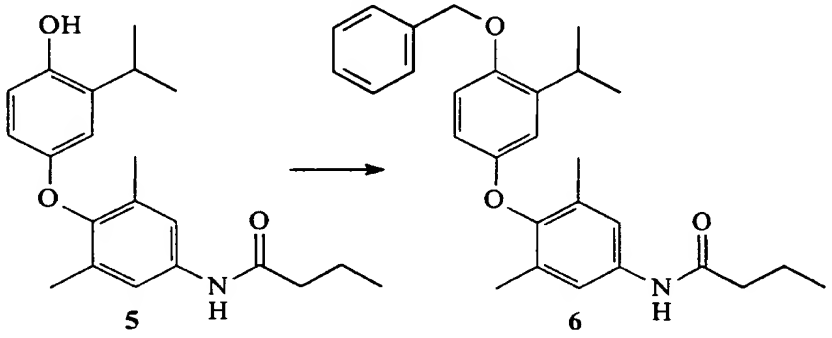
4. *N*-[3,5-dimethyl-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenyl]butyramide: Pyridine (4.3 mL) is added and 2',6'-dimethyl-3-*iso*-propyl-4-methoxy-4'-aminodiphenyl ether (**1d**, 4.3 g) is suspended therein. To this solution is added butyric anhydride (2.5 mL) and the reaction is stirred overnight. The sample is concentrated under reduced pressure and dissolved in ethyl acetate. This is extracted with 120 mL 0.15 N sodium hydroxide twice, washed with water, extracted twice with 150 mL 0.35 N hydrochloric acid, once with water and once with brine. The sample is dried over sodium sulfate and concentrated under reduced pressure. The residue is recrystallized from ethyl acetate:hexanes to afford amide **4**.

Example 5



5. *N*-[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenyl]butyramide: *N*-[3,5-dimethyl-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenyl]butyramide) (Example 4, 0.5 g) is dissolved in 5 mL dichloromethane and cooled in a dry ice/*iso*-propanol bath. To this solution is added dropwise 1 M boron tribromide (4.6 mL) in dichloromethane. After 30 minutes, the reaction is poured over ice (10 g) and is stirred an additional 30 minutes. At this time, 20 mL brine is added and stirred 20 minutes. The organic phase is separated and washed with brine. The aqueous phase is extracted once with ethyl acetate (10 mL) then the ethyl acetate layer is extracted with brine. The organic phases are combined and dried over sodium sulfate and concentrated under reduced pressure. The product is purified by chromatography on silica gel to afford **5**.

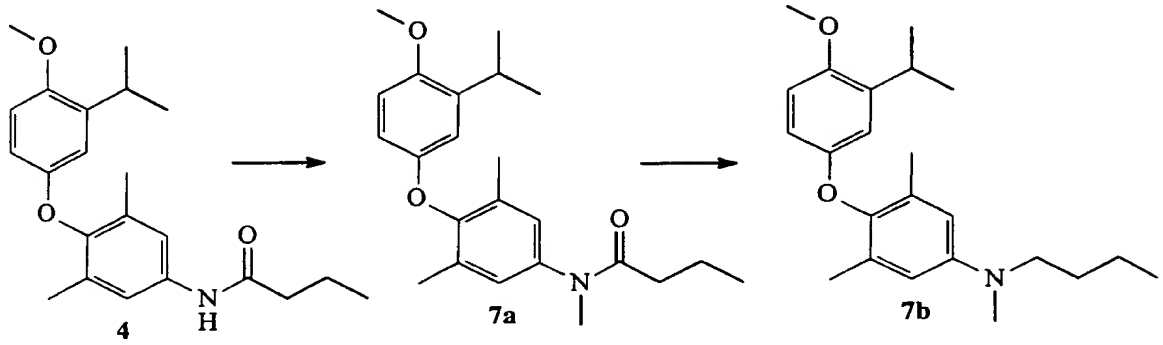
Example 6



6. *N*-[3,5-dimethyl-4-(4'-benzyloxy-3'-*iso*-propylphenoxy)phenyl]butyramide: *N*-[3,5-dimethyl-4-(4'-hydroxy-3'-*iso*-propylphenoxy)phenyl]butyramide) (Example **5**, 173 mg) is dissolved in 5 mL acetone. To this solution is added 96 mg potassium carbonate and 51 microliters benzyl bromide. The reaction is refluxed overnight. At this time, it is filtered

through celite and concentrated under reduced pressure. The product is crystallized from hexanes to afford **6**.

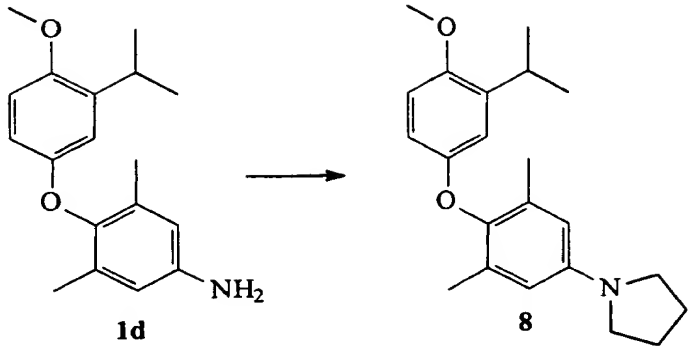
Example 7



7a. ***N*-methyl-*N*-[3,5-dimethyl-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenyl]butyramide:** In a dry flask under nitrogen, 0.34 g sodium hydride is suspended in 5 mL THF and stirred 10 minutes. To this solution is added dropwise *N*-[3,5-dimethyl-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenyl]butyramide) (Example **4**, 1 g) in 5 mL THF. The reaction is stirred for 15 minutes and methyl iodide, 0.3 mL is added dropwise. After 2 hours, the reaction is poured into ice water and extracted with chloroform. The organic layer is washed once with water, once with brine then dried over magnesium sulfate and concentrated under reduced pressure. The product is purified by chromatography on silica gel to afford **7a**.

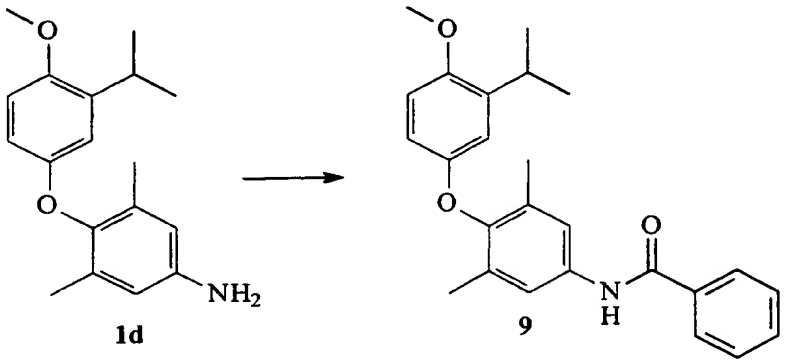
7b. ***N*-methyl-*N*-[3,5-dimethyl-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenyl]butylamine:** In a dry flask under nitrogen is placed lithium aluminum hydride (1.1 g). To this solid is added 30 mL THF dropwise. After stirring 10 minutes, a solution of *N*-methyl-*N*-[3,5-dimethyl-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenyl]butyramide (**7b**; 1.37 g) in 6 mL THF is added dropwise and the reaction is refluxed overnight. At this time, the reaction is cooled in an ice bath and 12 mL water is added dropwise followed by dropwise addition of 12 mL 15% sodium hydroxide then 60 mL water. The reaction is stirred for 90 minutes. At this time, it is filtered through celite and washed with THF and ethyl acetate. The filtrate is concentrated under reduced pressure and the product is purified by chromatography on silica gel to afford **7b**.

Example 8



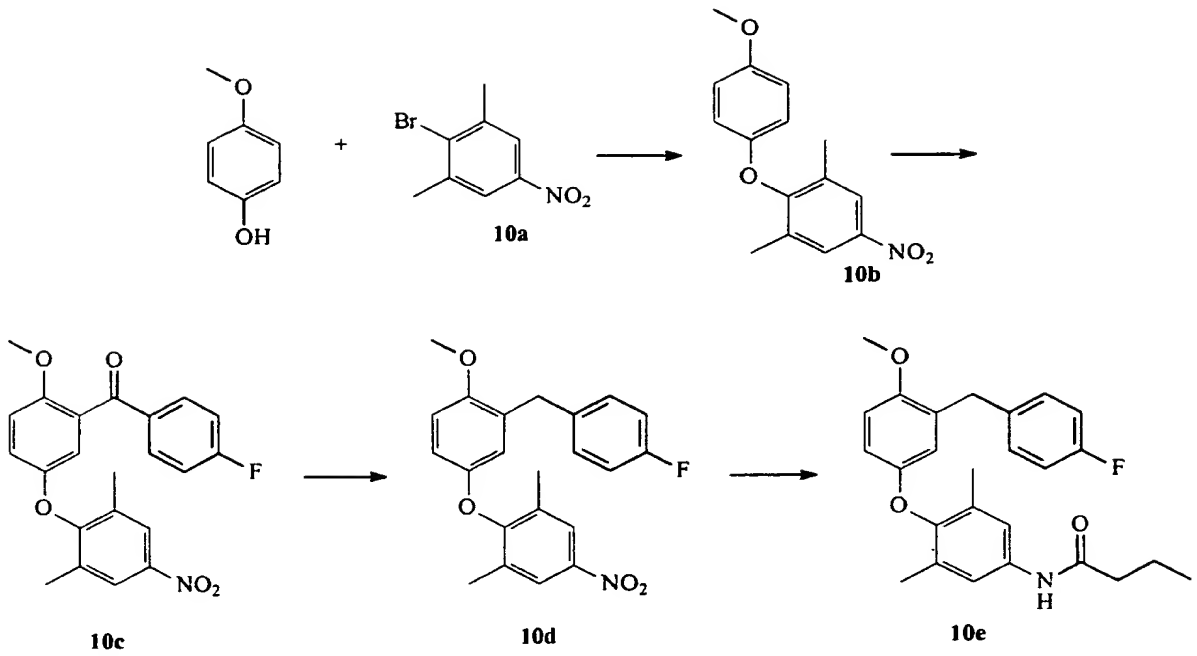
8. ***N*-[3,5-dimethyl-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenyl]pyrrolidine:** 2',6'-Dimethyl-3-*iso*-propyl-4-methoxy-4'-aminodiphenyl ether (**1d**, 1.5 g) is dissolved in 2 mL ethanol and 0.75 mL 1,4-diiodobutane is added. The sample is refluxed overnight. At this time, it is concentrated under reduced pressure. The sample is taken up in ethyl acetate and extracted with 0.1 N sodium hydroxide, water, and brine. After drying over sodium sulfate, filtering, and concentration under reduced pressure, the tertiary amine is purified by chromatography on silica gel to afford **8**.

Example 9



9. ***N*-[3,5-dimethyl-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenyl]benzamide:** Pyridine (1 mL) is added and 2',6'-dimethyl-3-*iso*-propyl-4-methoxy-4'-aminodiphenyl ether (Example **1d**, 0.23 g) is suspended therein. To this solution is added 0.24 mL benzoyl chloride and the reaction is stirred for about 1 hour. The sample is concentrated under reduced pressure and dissolved in ethyl acetate. This is washed with water and brine then dried over magnesium sulfate and concentrated under reduced pressure. The residue is recrystallized to afford **9**.

Example 10



10a. 4-bromo-3,5-dimethyl-nitrobenzene: 2',6'-dimethyl-4-nitrophenol (3 g) is added to 50 mL dichloromethane followed by addition of 3.6 mL pyridine. The solution is cooled to 0 °C and 3.6 mL trifluoromethanesulfonic anhydride is added dropwise over 20 minutes. The reaction is mixed for about 3 hours at 0 °C. Water (25 mL) is added to quench the reaction. The organic layer is extracted twice with 1N hydrochloric acid (25 mL), twice with water (25 mL), twice with 1N sodium hydroxide (25 mL), twice with water (25 mL), dried with magnesium sulfate, and concentrated under reduced pressure. The remaining residue is dissolved in 40 mL of DMF followed by addition of lithium bromide (4.7 g). The mixture is refluxed for 17 hours at 150°C. The mixture is concentrated under high vacuum. To this residue, 60 mL water and 60 mL ethyl acetate is added and stirred. This mixture is filtered, the organic layer separated and dried with magnesium sulfate. The organic layer is concentrated under high vacuum and the remaining residue presorbed to silica gel using dichloromethane. The presorbed residue is then purified by chromatography on silica gel and subsequently crystallized from hexanes to afford **10a**.

10b. 3,5-dimethyl-4-(4'-methoxyphenoxy)-nitrobenzene: 4-bromo-3,5-dimethyl-nitrobenzene (**10a**, 175 mg) and 4-methoxyphenol (94 mg) are dissolved into 7.5 mL dimethylsulfoxide. To this solution, anhydrous potassium carbonate (153 mg) is added and the

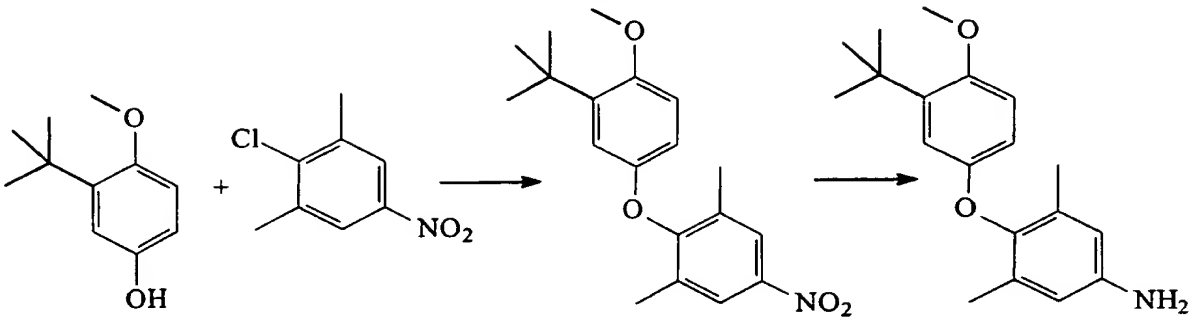
reaction mixed for 23 hours at about 130 °C. After 23 hours the reaction is precipitated by the addition of 50 mL ice water. The mixture is then extracted with 75 mL ethyl acetate. The organic layer is extracted once with 50 mL brine solution, dried with magnesium sulfate, and concentrated under high vacuum to afford **10b**.

10c. [5-(2,6-dimethyl-4-nitrophenoxy)-2-methoxyphenyl](4-fluorophenyl)methanone: 4-fluorobenzoyl chloride (137 mg) is dissolved in 2.5 mL dichloromethane followed by the addition of 77 microliters trifluoromethanesulfonic acid. After 5 minutes of mixing 3,5-dimethyl-4-(4'-methoxyphenoxy)-nitrobenzene (**10b**, 182 mg), is added and mixed for 15 hours. The reaction is concentrated under high vacuum and the remaining residue is presorbed to silica gel using dichloromethane. The presorbed residue is then purified by chromatography on silica gel to afford **10c**.

10d. 4-[3-(4-fluorobenzyl)-4-methoxyphenoxy]-3,5-dimethylnitrobenzene: [5-(2,6-dimethyl-4-nitrophenoxy)-2-methoxyphenyl](4-fluorophenyl)methanone (**10c**, 138 mg) is dissolved in 380 microliters of dichloromethane followed by the addition of 230 microliters TFA and 192 microliters triethylsilane. The reaction is mixed for 15 hours followed by an extraction with 20 mL diethyl ether and 10 mL water. The organic layer is extracted once with 20 mL of 5% sodium carbonate, once with 20 mL water, dried with magnesium sulfate, and concentrated under reduced pressure to afford **10d.**

10e. 4-[3-(4-fluorobenzyl)-4-methoxyphenoxy]-3,5-dimethyl-butyrylamidobenzene: 4-[3-(4-fluorobenzyl)-4-methoxyphenoxy]-3,5-dimethylnitrobenzene (**10d**, 138 mg) is dissolved in 5 mL ethanol. To this mixture, 18.4 mg of 10% palladium on carbon is added. The reaction is hydrogenated for 3 hours, then filtered through Celite and concentrated under reduced pressure. Pyridine (91 microliters) and butyric anhydride (184 microliters) are added to the residue and the reaction is stirred overnight. The reaction mixture is concentrated under high vacuum and purified by chromatography on silica gel to afford **10e**.

Example 11



11a **11b** **11c**

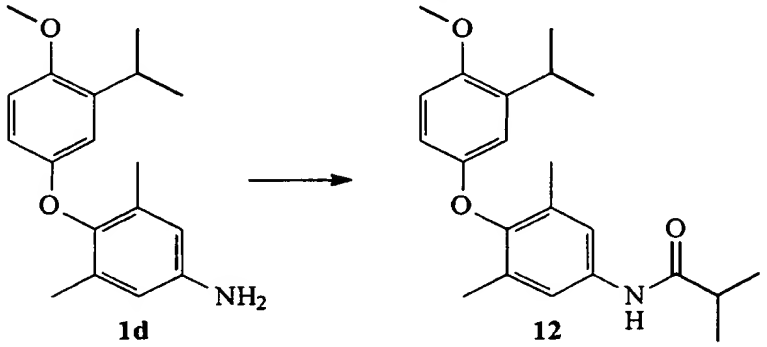
11a. 4-chloro-3,5-dimethyl-nitrobenzene: 2',6'-Dimethyl-4-nitrophenol (10 g) is added to 100 mL dichloromethane followed by the addition of 5.8 mL of pyridine. The solution is cooled to -2 °C and 12.1 mL trifluoromethanesulfonic anhydride is added dropwise over 1 hour. The reaction is stirred for about 3.5 hours at -2 °C. At this time, 50 mL ice water is added. The organic layer is extracted twice with 50 mL 1N hydrochloric acid, twice with 50 mL water, twice with 50 mL 1N sodium hydroxide, twice with 50 mL water, dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The residue is dissolved in 160 mL of 1-methyl-2-pyrrolidinone followed by addition of lithium chloride (3.6 g). The mixture is refluxed for 17 hours at 120 °C. The mixture is concentrated under reduced pressure. To this residue, 100 mL water and 100 mL ethyl acetate is added and stirred. This mixture is filtered, the organic layer separated, and dried with magnesium sulfate. The organic layer is concentrated under high vacuum to afford **11a**.

11b. 3,5-dimethyl-4-(4'-methoxy-3'-*tert*-butylphenoxy)-nitrobenzene: 4-Chloro-3,5-dimethyl-nitrobenzene (**11a**, 1.83 g) and 2-*tert*-butyl-4-hydroxyanisole (1.8 g) are dissolved in 15 mL dimethylsulfoxide. To this solution, anhydrous potassium carbonate (1.51 g) is added and the reaction stirred for 17 hours at 120 °C. The reaction is then cooled to 40 °C and poured into ethyl acetate (50 mL). The organic layer is then washed with ice water (50 mL), dried over magnesium sulfate and concentrated under reduced pressure. The residue is presorbed to silica gel using acetone. The presorbed residue is purified by chromatography on silica gel to afford **11b**.

11c. 3,5-dimethyl-4-(4'-methoxy-3'-*tert*-butylphenoxy)amino benzene: 3,5-Dimethyl-4-(4'-methoxy-3'-*tert*-butylphenoxy)-nitrobenzene (**11b**), 1.13 g, is dissolved in 25 mL ethanol and

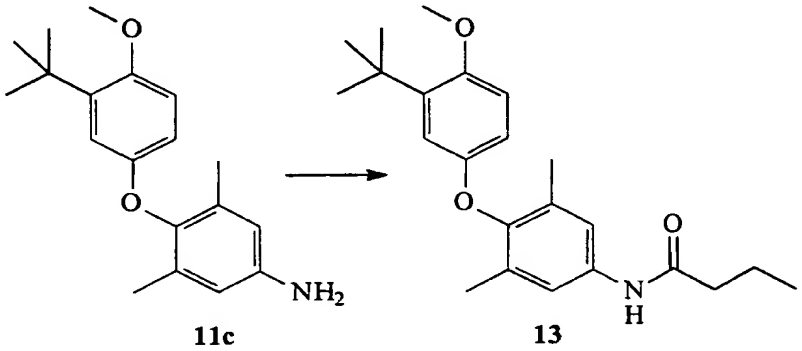
130 mg of 10% palladium on carbon is added. The reaction is hydrogenated for 1 hour, then filtered through a plug of silica gel and concentrated under reduced pressure to afford **11c**.

Example 12



12. ***N*-[3,5-dimethyl-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenyl]-2-methylpropionamide:** Isobutyric anhydride (4 mL) is added to 2',6'-dimethyl-3-*iso*-propyl-4-methoxy-4'-aminodiphenyl ether (**1d**, 0.21 g) and the reaction is stirred overnight. At this time, 20 mL water and 20 mL ethyl acetate are added and the reaction mixture is extracted with 1 N NaOH until the aqueous layer has a pH above 10. After extracting once with brine, drying over magnesium sulfate and filtering, the organic layer is concentrated under reduced pressure and purified by chromatography on silica gel to afford **12**.

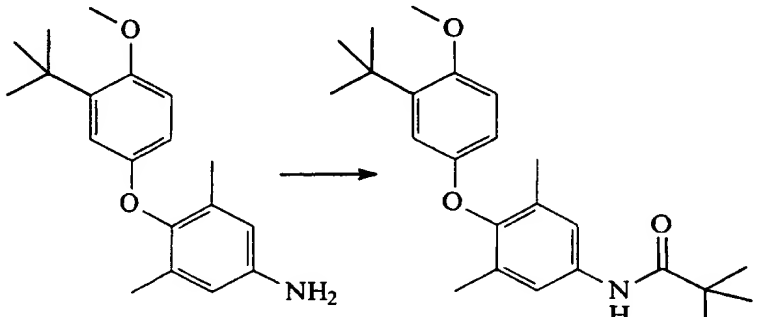
Example 13



13. ***N*-[3,5-dimethyl-4-(4'-methoxy-3'-*tert*-butylphenoxy)phenyl]butyramide:** 3,5-dimethyl-4-(4'-methoxy-3'-*tert*-butylphenoxy)amino benzene (**11c**, 1.1 g) is suspended in pyridine (0.6 mL) and butyric anhydride (1.2 mL) is added and the reaction is stirred for 30 minutes under nitrogen. The mixture is concentrated under reduced pressure and the residue is taken up in

ethyl acetate (30 mL). This material is then washed twice with 0.1N HCl (30 mL), water (30 mL), twice with 0.1N NaOH (30 mL), water (30 mL), and brine (30 mL). The organic layer is dried over magnesium sulfate, filtered, and the filtrate is concentrated under reduced pressure. The material is crystallized from hexanes to afford **13**.

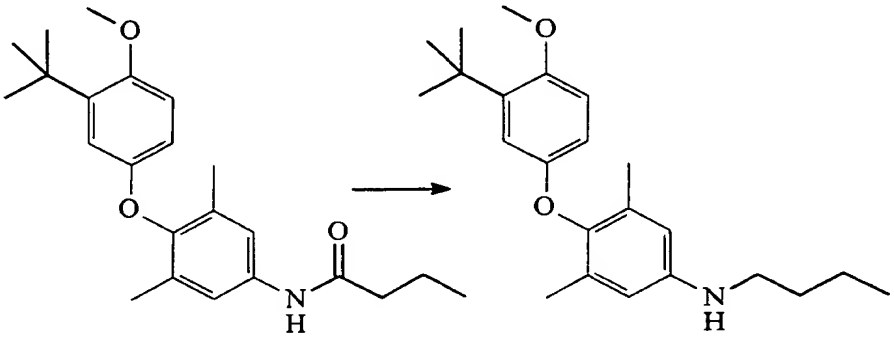
Example 14



11c **14**

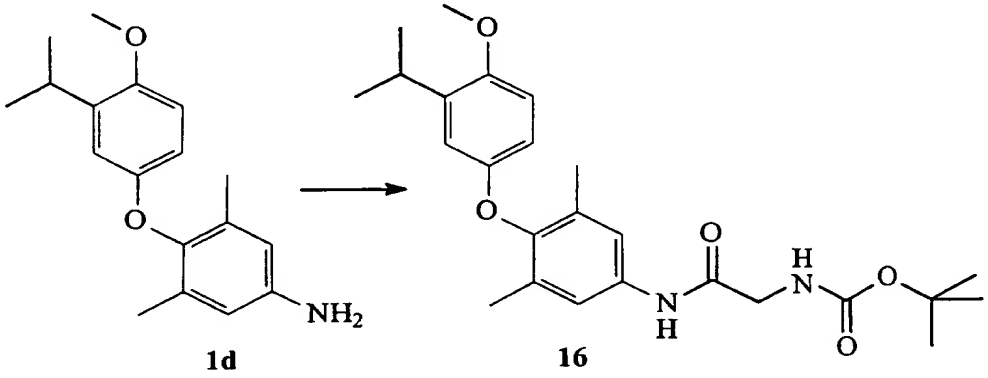
14. *N*-[3,5-dimethyl-4-(4'-methoxy-3'-*tert*-butylphenoxy)phenyl]trimethylacetamide: 3,5-Dimethyl-4-(4'-methoxy-3'-*tert*-butyl phenoxy)amino benzene (**11c**, 1.12 g) is suspended in pyridine (0.6 mL). To this solution is added trimethylacetyl chloride (0.9 mL) and the reaction is stirred overnight. The sample is concentrated under reduced pressure and dissolved in ethyl acetate (100 mL). This is washed with 100 mL 0.1 N sodium hydroxide twice, water (100 mL), 100 mL 0.1 N hydrochloric acid twice, water (100 mL) and brine (100 mL). The organic layer is dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue is presorbed to silica gel using acetone and purified by chromatography on silica gel to afford **14**.

Example 15



15. ***N*-[3,5-dimethyl-4-(4'-methoxy-3'-*tert*-butylphenoxy)phenyl] butylamine:** *N*-[3,5-dimethyl-4-(4'-methoxy-3'-*tert*-butylphenoxy)phenyl]butyramide (**13**, 0.43 g) is dissolved in THF (10 mL) and added dropwise to a solution of lithium aluminum hydride (0.3 g) in THF (30 mL) under nitrogen and allowed to react for two hours. The reaction is cooled in an ice bath and water (10 mL) is added dropwise. The precipitate which forms is filtered off and the filtrate is concentrated under reduced pressure. The filtrate is purified by chromatography on silica gel to afford **15**.

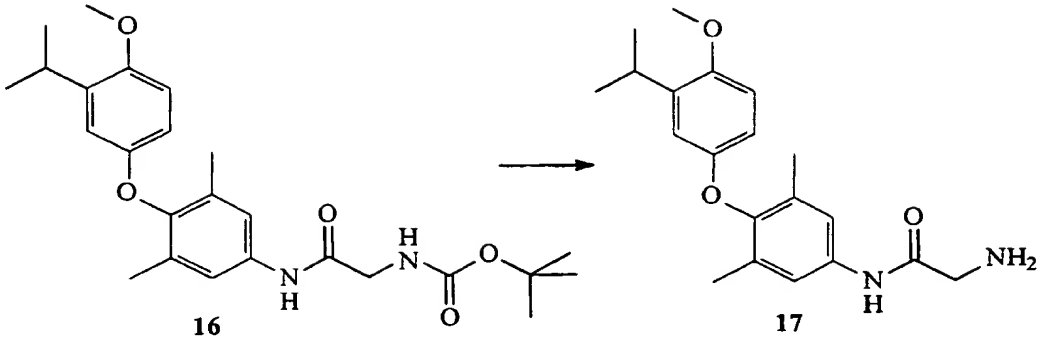
Example 16



1d **16**

16. **(*N*-[3,5-dimethyl-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenyl])-*N*-BOC-glycinamide:** 2',6'-dimethyl-3-*iso*-propyl-4-methoxy-4'-aminodiphenyl ether (**1d**, 0.44 g) and *N*-BOC-glycine (0.27 g) is suspended in 3 mL dichloromethane. To this is added 0.4 mL i-Pr_2EtN. After mixing, O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (0.58 g) is added and the reaction is stirred overnight. The reaction is diluted with 75 mL diethyl ether and the organic layer is washed with 2M potassium hydrogen sulfate (25 mL x 3), once with water, 1 N sodium hydroxide (50 mL x 2), and once with 50 mL brine. The organic layer is dried over sodium sulfate, filtered and the filtrate is concentrated under reduced pressure and purified by chromatography on silica gel to afford **16**.

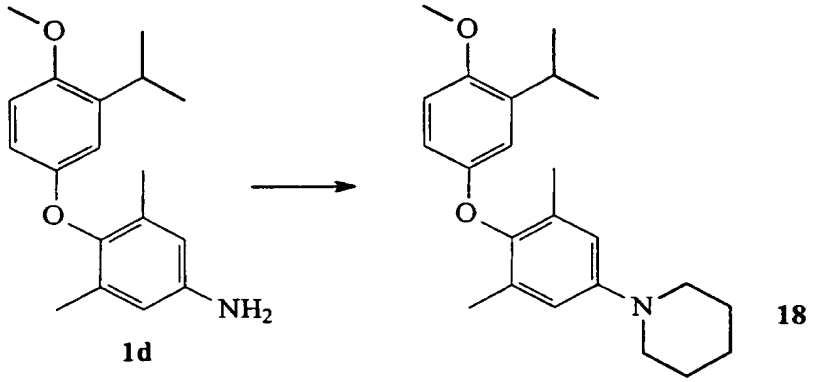
Example 17



16 17

17. (*N*-[3,5-dimethyl-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenyl])glycinamide: (*N*-[3,5-dimethyl-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenyl])glycinamide (**16**, 0.175 g) is dissolved in 1 mL dichloromethane and 0.31 mL TFA. The reaction stirred for 1 hour. At this time, the sample is diluted with 25 mL diethyl ether and washed twice with 10 mL 1N sodium hydroxide and once with 25 mL brine. The organic layer is dried over sodium sulfate, filtered, and the filtrate is concentrated under reduced pressure to afford **17**.

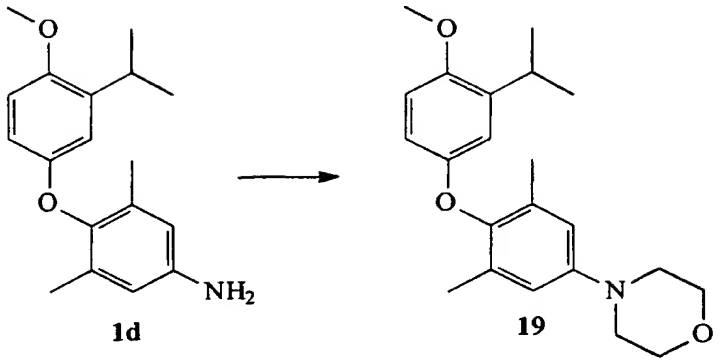
Example 18



1d 18

18. *N*-[3,5-dimethyl-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenyl]piperidine: 2',6'-Dimethyl-3-*iso*-propyl-4-methoxy-4'-aminodiphenyl ether (**1d**, 0.275 g) is dissolved in 1 mL ethanol and 0.142 mL 1,5-diiodopentane is added. The sample is refluxed for 4 hours. At this time, it is concentrated under reduced pressure. The sample is taken up in ethyl acetate and extracted with 0.1 N sodium hydroxide, water and brine. After drying over sodium sulfate, filtering, and concentrating the filtrate under reduced pressure, it is purified by chromatography on silica gel to afford **18**.

Example 19



19. ***N*-[3,5-dimethyl-4-(4'-methoxy-3'-*iso*-propylphenoxy)phenyl]morpholine:** 2',6'-Dimethyl-3-*iso*-propyl-4-methoxy-4'-aminodiphenyl ether (**1d**, 0.25 g) is dissolved in 2 mL ethanol and 0.150 g di(2-iodoethyl)ether is added. The sample is refluxed overnight. At this time, it is concentrated under reduced pressure. The sample is taken up in ethyl acetate and extracted with 0.1 N sodium hydroxide, water, and brine. After drying over sodium sulfate, filtering, and concentrating the filtrate under reduced pressure, it is purified by chromatography on silica gel to afford **19**.

Use of the Present Compounds

According to the methods of the present invention, a compound having a structure as described herein is administered, most preferably with a pharmaceutically-acceptable or cosmetically-acceptable carrier.

The compounds of the present invention may be used for the treatment of such conditions as treating hair loss in mammals, including arresting and / or reversing hair loss and promoting hair growth. Such conditions may manifest themselves in, for example, alopecia, including male pattern baldness and female pattern baldness.

In addition, the compounds of the present invention may be useful for weight control, including the treatment and / or prevention of obesity. Other uses for the compounds of the present invention include stimulation of nail growth, treatment of skin conditions, prevention of hair discoloration, obesity, cholesterol lowering, treatment of thyroid disorders, and treatment of osteoporosis.

Preferably the compounds of the present invention are, as defined herein, cardiac-sparing.

Preferably, the compounds are formulated into pharmaceutical or cosmetic compositions for use in treatment or prophylaxis of conditions such as the foregoing. Standard pharmaceutical formulation techniques are used, such as those disclosed in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. (1990).

Typically, from about 5 mg to about 3000 mg, more preferably from about 5 mg to about 1000 mg, more preferably from about 10 mg to about 100 mg, of a compound having a structure as described herein is administered per day for systemic administration. It is understood that these dosage ranges are by way of example only, and that daily administration can be adjusted depending on various factors. The specific dosage of the compound to be administered, as well as the duration of treatment, and whether the treatment is topical or systemic are interdependent. The dosage and treatment regimen will also depend upon such factors as the specific compound used, the treatment indication, the efficacy of the compound, the personal attributes of the subject (such as, for example, weight, age, sex, and medical condition of the subject), compliance with the treatment regimen, and the presence and severity of any side effects of the treatment.

According to the present invention, the subject compounds are co-administered with a pharmaceutically-acceptable or cosmetically-acceptable carrier (herein collectively described as "carrier"). The term "carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a mammal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with a compound of the present invention, and with each other, in a manner such that there is no interaction which would substantially reduce the efficacy of the composition under ordinary use situations. Carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the animal, preferably mammal (most preferably human), being treated. The carrier can itself be inert or it can possess pharmaceutical and / or cosmetic benefits of its own.

The compositions of this invention may be in any of a variety of forms, suitable (for example) for oral, rectal, topical, nasal, ocular or parenteral administration. Of these, topical and / or oral administration are especially preferred with topical being most preferred. Depending upon the particular route of administration desired, a variety of carriers well-known in the art may be used. These include solid or liquid fillers, diluents, hydrotropes, surface-active agents, and encapsulating substances. Optional pharmaceutically-active or cosmetically-active materials may be included which do not substantially interfere with the activity of the compound of the present invention. The

amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods of this invention are described in the following references: Modern Pharmaceutics, Chapters 9 and 10, Banker & Rhodes, eds. (1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms, 2nd Ed., (1976).

Some examples of substances which can serve as carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the TWEENS; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

The choice of a carrier to be used in conjunction with the subject compound is typically determined by the way the compound is to be administered.

In particular, carriers for systemic administration include sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffer solutions, emulsifiers, isotonic saline, and pyrogen-free water. Preferred carriers for parenteral administration include propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame oil. Preferably, the carrier, in compositions for parenteral administration, comprises at least about 90% by weight of the total composition.

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. These oral forms comprise a safe and effective amount, usually at least about 5%, and preferably from about 25% to about 50%, of a compound used in the present invention. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, containing

suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents.

The carriers suitable for the preparation of unit dosage forms for oral administration are well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmelose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules (including time release and sustained release formulations) typically comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of the subject invention, and can be readily made by a person ordinarily skilled in the art.

Orally administered compositions also include liquid solutions, emulsions, suspensions, powders, granules, elixirs, tinctures, syrups, and the like. The carriers suitable for preparation of such compositions are well known in the art. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, AVICEL RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose.

Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

The compounds of the present invention may also be topically administered. The carrier of the topical composition preferably aids penetration of the present compounds into the skin to reach the environment of the hair follicle. Topical compositions of the present invention may be in any form including, for example, solutions, oils, creams, ointments, gels, lotions, shampoos, leave-on and rinse-out hair conditioners, milks, cleansers, moisturizers, sprays, skin patches, and the like.

Topical compositions containing the active compound can be admixed with a variety of carrier materials well known in the art, such as, for example, water, alcohols, aloe vera gel, allantoin, glycerine, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate, and the like.

Other materials suitable for use in topical carriers include, for example, emollients, solvents, humectants, thickeners and powders. Examples of each of these types of materials, which can be used singly or as mixtures of one or more materials, are as follows:

Emollients, such as stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, *iso*-propyl isostearate, stearic acid, *iso*-butyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, dimethylpolysiloxane, di-*n*-butyl sebacate, *iso*-propyl myristate, *iso*-propyl palmitate, *iso*-propyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, and myristyl myristate; propellants, such as propane, butane, *iso*-butane, dimethyl ether, carbon dioxide, and nitrous oxide; solvents, such as ethyl alcohol, methylene chloride, *iso*-propanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, methylsulfoxide, dimethyl formamide, tetrahydrofuran; humectants, such as glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, and gelatin; and powders, such as chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically modified magnesium aluminium silicate, organically modified montmorillonite clay, hydrated aluminium silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, and ethylene glycol monostearate.

The compounds used in the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines. A preferred formulation for topical delivery of the present compounds utilizes liposomes such as described in Dowton et al., "Influence of Liposomal Composition on Topical Delivery of Encapsulated Cyclosporin A: I. An *in vitro* Study Using Hairless Mouse Skin", *S.T.P. Pharma Sciences*, Vol. 3, pp. 404 - 407 (1993); Wallach and Philippot, "New Type of Lipid Vesicle: Novasome®", Liposome Technology, Vol. 1, pp. 141 - 156 (1993); Wallach, U.S. Patent No. 4,911,928, assigned to Micro-Pak, Inc., issued March 27, 1990; and Weiner et al., U.S. Patent No. 5,834,014, assigned to The University of Michigan and Micro-Pak, Inc., issued November 10, 1998 (with respect to Weiner et al., with a compound as described herein administered in lieu of, or in addition to, minoxidil).

The compounds of the present invention may also be administered by iontophoresis. See, e.g., internet site www.unipr.it/arpa/dipfarm/erasmus/erasm14.html; Banga et al., "Hydrogel-based Iontotherapeutic Delivery Devices for Transdermal Delivery of Peptide/Protein Drugs", *Pharm. Res.*, Vol. 10 (5), pp. 697-702 (1993); Ferry, "Theoretical Model of Iontophoresis Utilized in Transdermal Drug Delivery", *Pharmaceutical Acta Helvetiae*, Vol 70, pp. 279-287 (1995); Gangarosa et al., "Modern Iontophoresis for Local Drug Delivery", *Int. J. Pharm*, Vol. 123, pp. 159-171 (1995); Green et al., "Iontophoretic Delivery of a Series of Tripeptides Across the Skin *in vitro*", *Pharm. Res.*, Vol 8, pp. 1121-1127 (1991); Jadoul et al., "Quantification and Localization of Fentanyl and TRH Delivered by Iontophoresis in the Skin", *Int. J. Pharm.*, Vol. 120, pp. 221-8 (1995); O'Brien et al., "An Updated Review of its Antiviral Activity, Pharmacokinetic Properties and Therapeutic Efficacy", *Drugs*, Vol. 37, pp. 233-309 (1989); Parry et al., "Acyclovir Biovailability in Human Skin", *J. Invest. Dermatol.*, Vol. 98 (6), pp. 856-63 (1992); Santi et al., "Drug Reservoir Composition and Transport of Salmon Calcitonin in Transdermal Iontophoresis", *Pharm. Res.*, Vol 14 (1), pp. 63-66 (1997); Santi et al., "Reverse Iontophoresis - Parameters Determining Electroosmotic Flow: I. pH and Ionic Strength", *J. Control. Release*, Vol. 38, pp. 159-165 (1996); Santi et al., "Reverse Iontophoresis - Parameters Determining Electroosmotic Flow: II. Electrode Chamber Formulation", *J. Control. Release*, Vol. 42, pp. 29-36 (1996); Rao et al., "Reverse Iontophoresis: Noninvasive Glucose Monitoring *in vivo* in Humans", *Pharm. Res.*, Vol. 12 (12), pp. 1869-1873 (1995); Thysman et al., "Human Calcitonin Delivery in Rats by Iontophoresis", *J. Pharm. Pharmacol.*, Vol. 46, pp. 725-730 (1994); and Volpato et al., "Iontophoresis Enhances the Transport of Acyclovir through

Nude Mouse Skin by Electrorepulsion and Electroosmosis", *Pharm. Res.*, Vol. 12 (11), pp. 1623-1627 (1995).

The compositions used in the present invention may also optionally comprise an activity enhancer. The activity enhancer can be chosen from a wide variety of molecules which can function in different ways to enhance hair growth effects of a compound of the present invention. Particular classes of activity enhancers include other hair growth stimulants and penetration enhancers.

Non-limiting examples of other hair growth stimulants which may be used in the compositions herein, including both systemic and topical compositions, include, for example, benzalkonium chloride, benzethonium chloride, phenol, estradiol, diphenhydramine hydrochloride, chlorpheniramine maleate, chlorophyllin derivatives, cholesterol, salicylic acid, cysteine, methionine, red pepper tincture, benzyl nicotinate, D,L - menthol, peppermint oil, calcium pantothenate, panthenol, castor oil, hinokitiol, prednisolone, resorcinol, monosaccharides and esterified monosaccharides, chemical activators of protein kinase C enzymes, glycosaminoglycan chain cellular uptake inhibitors, inhibitors of glycosidase activity, glycosaminoglycanase inhibitors, esters of pyroglutamic acid, hexosaccharic acids or acylated hexosaccharic acids, aryl-substituted ethylenes, N-acylated amino acids, and, of course, minoxidil or finasteride. The most preferred activity enhancers are minoxidil and finasteride, most preferably minoxidil.

Non-limiting examples of penetration enhancers which may be used in the compositions herein include, for example, 2-methyl propan-2-ol, propan-2-ol, ethyl-2-hydroxypropanoate, hexan-2,5-diol, POE(2) ethyl ether, di(2-hydroxypropyl) ether, pentan-2,4-diol, acetone, POE(2) methyl ether, 2-hydroxypropionic acid, 2-hydroxyoctanoic acid, propan-1-ol, 1,4-dioxane, tetrahydrofuran, butan-1,4-diol, propylene glycol dipelargonate, polyoxypropylene 15 stearyl ether, octyl alcohol, POE ester of oleyl alcohol, oleyl alcohol, lauryl alcohol, dioctyl adipate, dicapryl adipate, di-isopropyl adipate, di-isopropyl sebacate, dibutyl sebacate, diethyl sebacate, dimethyl sebacate, dioctyl sebacate, dibutyl suberate, dioctyl azelate, dibenzyl sebacate, dibutyl phthalate, dibutyl azelate, ethyl myristate, dimethyl azelate, butyl myristate, dibutyl succinate, didecyl phthalate, decyl oleate, ethyl caproate, ethyl salicylate, *iso*-propyl palmitate, ethyl laurate, 2-ethyl-hexyl pelargonate, *iso*-propyl isostearate, butyl laurate, benzyl benzoate, butyl benzoate, hexyl laurate, ethyl caprate, ethyl caprylate, butyl stearate, benzyl salicylate, 2-hydroxypropanoic acid, 2-hyroxyoctanoic acid, methylsulfoxide, N,N-dimethyl acetamide, N,N-dimethyl formamide, 2-pyrrolidone, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, 1,5-

dimethyl-2-pyrrolidone, 1-ethyl-2-pyrrolidone, phosphine oxides, sugar esters, tetrahydrofurfural alcohol, urea, diethyl-*m*-toluamide, and, 1-dodecylazacycloheptan-2-one.

In all of the foregoing, of course, the compounds used in the present methods can be administered alone or as mixtures, and the compositions may further include additional drugs or excipients as appropriate for the indication.

The present invention further relates to kits comprising a compound and / or composition of the present invention and information and / or instructions by words, pictures, and / or the like, that use of the kit will provide treatment for hair loss in mammals (particularly humans) including, for example, arresting and / or reversing hair loss and / or promoting hair growth. In addition or in the alternative, the kit may comprise a compound and / or composition of the present invention and information and / or instructions regarding methods of application of the compound and / or composition, preferably with the benefit of treating hair loss in mammals.

Examples of Composition Administration

The following examples do not limit the invention, but provide guidance to the ordinarily skilled artisan to perform the methods of the present invention. In each example, a compound other than the one mentioned may be substituted in the example by another having a structure as described herein with similar results.

Example A

A composition for topical administration is made, comprising:

Component	Amount
Compound of Example 3	5 %
Ethanol	57 %
Propylene Glycol	19 %
Dimethyl Isosorbide	19 %

A human male subject suffering from male pattern baldness is treated by a method of this invention. Specifically, for 6 weeks, the above composition is daily administered topically to the subject.

Example B

A composition for topical administration is made according to the method of Dowton et al., "Influence of Liposomal Composition on Topical Delivery of Encapsulated Cyclosporin A: I. An *in vitro* Study Using Hairless Mouse Skin", S.T.P. Pharma Sciences, Vol. 3, pp. 404 - 407 (1993), using the compound of Example 2 in lieu of cyclosporin A and using the Novasome 1 for the non-ionic liposomal formulation.

A human male subject suffering from male pattern baldness is treated each day with the above composition. Specifically, for 6 weeks, the above composition is administered topically to the subject.

Example C

A shampoo is made, comprising:

	Ex. C-1	Ex. C-2	Ex. C-3	Ex. C-4
Component				
Ammonium Lauryl Sulfate	11.5 %	11.5 %	9.5 %	7.5 %
Ammonium Laureth Sulfate	4 %	3 %	2 %	2 %
Cocamide MEA	2 %	2 %	2 %	2 %
Ethylene Glycol Distearate	2 %	2 %	2 %	2 %
Cetyl Alcohol	2 %	2 %	2 %	2 %
Stearyl Alcohol	1.2 %	1.2 %	1.2 %	1.2 %
Glycerin	1 %	1 %	1 %	1 %
Polyquaternium 10	0.5 %	0.25 %	-	-
Polyquaternium 24	-	-	0.5 %	0.25 %
Sodium Chloride	0.1 %	0.1 %	0.1 %	0.1 %
Sucrose Polyesters of Cottonate Fatty Acid	3 %	3 %	-	-
Sucrose Polyesters of Behenate Fatty Acid	2 %	3 %	-	-
Polydimethyl Siloxane	-	-	3 %	2 %
Cocaminopropyl Betaine	-	1 %	3 %	3 %
Lauryl Dimethyl Amine Oxide	1.5 %	1.5 %	1.5 %	1.5 %
Decyl Polyglucose	-	-	1 %	1 %
DMDM Hydantoin	0.15 %	0.15 %	0.15 %	0.15 %
Compound of Example 1	-	3 %	3 %	-
Compound of Example 4	6 %	-	-	6 %
Minoxidil			3 %	2 %
Phenoxyethanol	0.5 %	0.5 %	0.5 %	0.5 %
Fragrance	0.5 %	0.5 %	0.5 %	0.5 %
Water	q.s.	q.s.	q.s.	q.s.

A human subject suffering from male pattern baldness is treated by a method of this invention. Specifically, for 12 weeks, the above shampoo is used daily by the subject.